NINCDS Monograph No. 24

THE NINCDS COLLABORATIVE STUDY OF BRAIN DEATH

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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As growth in many centers of the practice of organ transplantation continues, controversy surrounding the nature and definition of brain death also continues.

The National Institute of Neurological and Communicative Disorders and Stroke has long had an interest in this controversy, and in 1969-70 sponsored a collaborative study of brain death aimed at airing the problems facing any group attempting to propose uniform national standards. Virtually all of the data from that study have been published (see references). No single document, however, has summarized the salient findings and correlations in the form here presented, and this monograph is published in order to accomplish that end.

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U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
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National Institute of Neurological and
Communicative Disorders and Stroke
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THE NINDS COLLABORATIVE STUDY OF BRAIN DEATH

A Historical Perspective

by

Gaetano F. Molinari, M.D.

INTRODUCTION

Between July 1, 1971 and October 16, 1972, a total of 503 patients had been entered to a fixed protocol study of brain death, sponsored by the then National Institute of Neurological Diseases and Stroke (NINDS). These cases were intensively studied for etiology of coma, presenting neurological signs and electroencephalograms, and were followed at fixed intervals, using these same parameters until outcome. In fatal cases where autopsy was obtained, detailed neuropathological examinations were made of the brains for correlation with the clinical signs and symptoms, and course of the disease.

To date more than 40 publications have been derived either in toto or in part from the background material or the data base generated by that study. Two of these are book-length monographs, (8,82) and several papers have appeared as chapters in other book-length monographs, (45,78) and others (6,9,17,21,27,33,35,44,52,72,83,84) in the proceedings of a major symposium (32). The remainder are spread through a variety of general (13,14,64,65,66,67,70,74,75,80,81) and specialized medical journals (4,5,15,16,26,29,30,31,34,46,51,69,71,76,77,79). Others are still in preparation or in manuscript.

These various publications are presently being cited and appear in the references of other authors whose concepts and criteria for brain death may concur or conflict with ideas included in reports derived from the collaborative study.

Because of the fragmentation, and dissemination of reports derived from the Collaborative Study of Brain Death in various formats over the past several years, it is the purpose of this report to review the history and design of the study, its scientific rationale, its salient findings, and to identify the unresolved issues concerning "brain death" uncovered by that collaborative study. Since the data from that study are now finding their way into policy statements (69), review articles (11,12), and data have become subject to controversy, it seems advisable to set limits upon interpretation of the study in order to avoid misinterpretation and out of context citation.

As recently reported in the analysis by Black (11,12), dominant conceptualization of brain death in this country during the late 1960's and early 1970's was couched in physiological terms and defined as the state that exists when "the brain no longer functions and has no possibility of functioning again." This was the descriptive definition proffered by the Harvard Ad Hoc Committee on Irreversible Coma and widely accepted by American physicians.

Neuropathologically oriented scientists, however, (2,3,23,24,25, 43,85) held the view that a brain may be considered dead when a condition exists of extensive brain necrosis. Although developed and supported by some Americans, this pathoanatomical definition prevailed in Europe.

American thinking was greatly influenced by Silverman (60,61,62, 63), Schwab (59), Pribram (55), Radberg (56), and their associates, and was summarized in a series of papers specifying the utility of the electroencephalogram, the rigid technical conditions required to insure accurate EEG interpretations in brain death suspects and the rarity of survival among patients showing electrocerebral silence. In a survey of 279 electroencephalographers based upon 2,650 patients with one EEG showing electrocerebral silence, only three drug intoxicated patients improved, Silverman et al. (60).

Some literature also existed which showed widespread necrosis at autopsy in patients who fulfilled the "Harvard Criteria" (2,3). All series correlating clinical and pathological features were limited by numbers of patients and by the clinical perspectives of the investigations (10,25,46). Zander and Rabinowitz (85) published pathological findings on patients with an isoelectric EEG and profound fall in systemic blood pressure, and in a small series, Plum and Posner (53) indicated progressive circulatory collapse and loss of thermal control in addition to neurological criteria predict irreversible cardiac arrest within 50 hours; others focused on failure of cerebral circulation as the major criterion for brain death (19,20,22,23, 24, 28,42).

Although it was known that intracranial pressure could exceed carotid artery perfusion pressure and thus cause arrest of intracranial circulation (41,55,57), a survey of methods available to assess cerebral circulation was made early in the planning stages of the NINDS research program and published later in 1973 (67), from which it was concluded that no cerebral blood flow technique existed which would be practical for incorporation into an American collaborative prospective study.

Nonetheless, in 1972, the report of a symposium was published which advocated use of four vessel angiography as the confirmatory criterion for total brain infarction and thereby for brain death throughout Scandinavia (28). These recommendations were consistent with criteria proposed earlier in Germany (20) and France (19).

While some consensus may have developed over time, which would have reconciled the divergent opinions and definitions of brain death and the methods for diagnosis, the concurrent rapid development of human organ transplantation and specialized patient intensive care facilities seemed to demand a prompt resolution to the underlying central issue of

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the ability to pronounce death despite extraordinary, artificial, and often extravagant means of supporting the cardiorespiratory functions conventionally recognized as the vital signs. Although these ideas were not new to investigators, scientists, and specialists, the celebrity given by the media to the transplantation of a beating human heart by Dr. Christian Barnard in 1967, brought the issues to wide general medical, and indeed, public attention and concern.

PLANNING AND IMPLEMENTATION OF THE NINDS COLLABORATIVE STUDY

In June of 1970, the National Advisory Council for Neurological Diseases and Stroke, after reviewing a grant application submitted by Dr. Silverman to study the problem of cerebral death, decided that the scientific, medical, and social priority of the problem required a national effort to investigate the multiplicity of factors associated with brain death. Acting on the advice of the Council, the then director of NINDS, Dr. Edward F. MacNichol, instructed the Special Projects Branch of the Collaborative and Field Research Division of the NINDS (now NINCDS) to appoint an ad hoc advisory committee for the purpose of developing a program of research leading to improvement in the criteria for brain death. The ad hoc advisory committee was chaired by Dr. Richard L. Masland and included Dr. Gilbert Beebe, biostatistician; Dr. Albert Niden, pulmonary physiologist; Dr. E. Pearson Richardson, neuropathologist; Dr. Dan Silverman, neurologist and electroencephalographer; Dr. Herbert Jasper, electroencephalographer; and Mr. Blair Sadler, an attorney. All of these individuals had an interest in the general problem of brain death. In addition, the committee had at its disposal consulting services from experts in the field of cerebral circulation and other disciplines considered relevant to the issue, such as neurochemistry and pharmacology.

The advisory committee concluded, after its deliberations, that the initial step in a program of research should be a collaborative pilot study. A preliminary study was to be designed to test the feasibility of addressing the problem uniformly and scientifically at multiple locations by different investigators. They felt that depending upon the results of the pilot phase a definitive study might later be designed to test the reliability of the various indicators of brain death found significant in the pilot phase.

Based upon the recommendations and information gathered by the ad hoc advisory committee, the NINDS staff of the section on head injury of the Applied Neurology Branch formulated a protocol for the pilot phase. Because of the needs for a fixed protocol, for acquisition of standard data from every patient, and for intra as well as interinstitutional collaboration among various specialists, the contract mechanism was chosen for the review and funding of proposals.

In keeping with the contract format, goals and objectives of the research project were stated in terms of "specific aims" rather than rational or specific scientific hypotheses. Those specific aims were as follows (verbatim quotation):

1. To determine whether the contemplated neurological, encephalographic, and other appropriate examinations can be adequately handled in a collaborative study, and to establish a basis for achieving standardization;

2. To determine whether in a collaborating hospital any case of suspected cerebral death would be missed, and if so, why;

3. To develop means of determining when a clinical and electroencephalographic picture consistent with cerebral death is a result of sedative drug intoxication;

4. To develop procedures for the collection, review, editing and processing of data for a definitive study;

5. To evaluate means for guaranteeing uniformity in handling patients, making the necessary observations, and recording data for analysis;

6. To determine the minimal significant set of clinical, electroencephalographic, laboratory, and demographic observations that will be needed for each patient in the definitive study;

7. To determine the best criteria for describing patients suspected of cerebral death so that the risks associated with an operating rule for determining brain death can be estimated most efficiently from data gathered in the study.

8. To determine the sample size needed in a later study in order to obtain desired precisions of estimates with due regard for variability in the patient population with respect to age and etiology of coma; and

9. To create an executive capability that can be extended to a definitive study.

Among 29 applications submitted by potential investigators at institutions wishing to participate in the collaborative research program, eight clinical centers were selected. Dr. A. Earl Walker was chosen as the project coordinator and his location, the University of New Mexico, as the coordinating center. Project directors at the eight clinical centers were: Dr. Reginald Bickford, University of California, San Diego; Dr. David Poskanzer, Massachusetts General Hospital, Boston, Massachusetts; Dr. Francis McGee and later Dr. Cary Suter of Virginia Commonwealth University, Richmond, Virginia; Dr. Julius Korein, New York University, New York, New York; Dr. Benjamin Boshes, Northwestern University, Chicago; initially Dr. W. Wiederholt and then Dr. Norman Allen at Ohio State

University; Dr. Lorenzo Runk of the University of Pennsylvania Graduate Hospital, and Dr. Donald Bennett at the University of Utah. Raw data processing and statistical analyses were handled at The Johns Hopkins University by Dr. Earl Diamond, under subcontract with the University of New Mexico.

In June of 1972 the University of Pennsylvania withdrew from the study, and in July of 1972 the Massachusetts General Hospital discontinued new patient acquisition. After soliciting additional statements of interest and capability, the College of Physicians and Surgeons in New York entered the study in July, 1972, the project there to be directed by Dr. Eli Goldensohn. In August, 1972, I became the project officer for the study as the new chief of the section on head injury and stroke of the Applied Neurological Research Branch. In October of 1972, accession data on the first 503 patients was complete. A revised interim data collection program was begun, pending re-evaluation of the pilot phase by the ad hoc advisory committee on brain death. Approximately 115 additional patients were identified using the interim protocol, but data submitted was not uniform and these patients could not be pooled in the analysis of the first 503 cases.

STUDY DESIGN

By design the research was planned as a "non-intervention" study. The investigators were not to declare brain death or make decisions regarding termination of artificial respiration. Pronouncement of death was always left to the responsible physicians who in turn were left apparently to their own knowledge of the current literature as to what criteria should be met in pronouncing death. The prevailing criteria in use in this country were the Harvard Criteria which required two EEG's twenty-four hours apart in confirmation of clinical criteria.

Although the research directors themselves did not make decisions to terminate or to continue respirator support, a most critical parameter used by others in decision making was provided by these investigators; namely, the EEG and its interpretation, since in most centers they were also the clinical electroencephalographers. Residents and neurological associates of the project investigators were often involved as consultants to the responsible primary physicians. Occasionally such consultants were the same individuals responsible for gathering the clinical data for the project.

Since the project was not an intervention study, "death" was reached at either of two end points: either cardiorespiratory support was terminated by the responsible physician after his pronouncement of brain death using criteria which were not controlled by the study investigators; or, patients were continued on respirators with all other means of life support to the point of spontaneous cardiac arrest.

The study was therefore a survey of criteria in common use by doctors, since pronouncement of death was not controlled by the research teams.

For accession to the study, patients met only two criteria (1) deep unresponsive coma and (2) apnea. Apnea, as reported in the summary statement derived from the collaborative study, was defined "for the purposes of this study as the absence of spontaneous respiration, manifested by the need for controlled ventilation--that is, the patient made no effort to override the respirator for at least 15 minutes" (81). Although aware of the possibility for using pure oxygen followed by safe termination of the respirator for relatively prolonged periods (39) in order to test for apnea as advocated, subsequently it was judged impractical to do this and the operational definition of apnea cited above was accepted by all of the study investigators.

The protocol called for an initial assessment, including standardized procedures for estimation of level of consciousness, presence or absence of cephalic reflexes, spinal reflexes, and the EEG. These were each repeated at six hourly intervals until either ECS (electrocortical silence) or improvement occurred. Once an EEG demonstrated electrocerebral silence, examinations were to be repeated at 6, 12, 24, 48 and 72 hours, and thereafter daily until death or improvement. Patients were "improved" if they became responsive to stimuli or regained spontaneous respiration. Responsible physicians were not required to pronounce death after any given number of EEG's showing electrocerebral silence, nor were they required to use any given set of criteria in pronouncement of death. Therefore, three end points were possible: (1) termination of artificial resuscitation by the physician, (2) cardiac arrest despite continued use of respirator, and (3) survival defined within the study as alive at last contact, three months after meeting accession criteria.

The protocol required each EEG to be performed in the standard format prescribed by the American Electroencephalographic Society (60), and required detailed standard pathological sections and stains made for microscopic studies on all brain specimens obtained at autopsy.

Review panels of expert electroencephalographers and neuropathologists who were not involved directly in the investigation at clinical centers were appointed and met at regular intervals. The purpose of these review panels was to insure quality control in data acquisition and interpretation. Random samples of EEG's or pathological slides already interpreted at local centers were reviewed; review panels were also to resolve controversial or equivocal interpretations of selected specimens of known ambiguity. These panels were set up because despite the standardization and coding of clinical, EEG and pathological data for computerized reduction and analysis, all parameters tested required subjective observation and interpretation prior to coding and subsequent objective, quantitative analysis.

CRITIQUE OF STUDY DESIGN

Although the study which was performed and completed had been intended from the start to be a pilot study, and contained no explicit hypotheses, a careful reading of the protocol indicates that it was, in fact, designed as a prospective test of the Harvard Criteria; the implicit hypothesis was to see which subset of the Harvard Criteria would correlate with incontrovertible evidence of total brain destruction by autopsy within minimum time after onset of coma. While Black's analysis dissects the two diverse conceptualizations of brain death into the non-functioning brain with no chance of recovery and total brain necrosis (11,12), the NINDS Collaborative Study of Brain Death incorporated both concepts.

Comatose apneic patients would either survive or die. Of the fatal cases, some would have been pronounced "brain dead" by their own physicians, who then terminated resuscitation. The others would have died of cardiac arrest despite continuous respiratory resuscitation. Clinical and EEG parameters were expected to identify the survivors as well as the dead.

Autopsy evidence was expected to prove the accuracy of the diagnosis of brain death in patients meeting the minimal subset criteria which were the subject of study. Although pathological changes generally lag behind irreversible physiological and biochemical changes, in a large enough sample, statistical correlations might be made within subsamples, even though time on respirator was not a controlled variable and was itself a subject of the study. Predictors of total brain destruction might be found.

If certain combinations of clinical and EEG findings were found always to correlate with anatomical evidence of brain death at autopsy after a given time interval, those combinations could be used or tested in subsequent studies as criteria for death. Once validated pathologically, in a large statistically significant sample, the clinical criteria need not be validated in every instance used.

The clinical and EEG changes then would not predict death but rather predict anatomical confirmation of death if the pathogenesis were allowed to run its course. Given such clinical and EEG predictors, death might be pronounced when the predictive criteria were met, and need not be delayed until the time when an autopsy would invariably show total brain destruction.

The study design depended upon validation of the clinical and EEG criteria by gross and light microscopic changes of irreversible destruction of brain.

By following the course of comatose apneic patients to outcome without interference, the same study did permit observation of predictors of survival, or predictors of death, independent of the criteria used in pronouncing death.

ANCILLARY PROJECTS

Although the need for uniform data collection on a fixed protocol seemed to be the overriding concern for the pilot phase, to some participants, the exclusion of blood flow studies and of other potential confirmatory techniques seemed restrictive. Each participating investigator was therefore encouraged to develop an ancillary project which might be unique to that particular center, but which should not interfere with the acquisition of reliable core data required by the fixed protocol and which could succeed or fail without jeopardy to the core study. Such ancillary studies (82,83) included electroretinography (64), computerized EEG analyses, spinal fluid analyses (49), comprehensive drug screening and quantitative analyses for CNS depressant drugs (80). Two ancillary projects require specific comment.

An ancillary study, developed at New York University, involved the exploration of an intravenous isotope bolus injection while simultaneous monitoring over the brow and over the femoral artery with specially collimated sodium iodide crystals in order to show presence or absence of bolus transit curves over the brain compared to a control artery (15,16). The other study requiring special comment was an ancillary project set up at the NINDS, on testing for substances in the blood (80,81,82), known to depress EEG activity and/or respiration as well as consciousness. The fixed protocol required only blood barbiturate levels to be drawn and analyzed locally on every patient entered into the study. However, in each case the blood barbiturate sample was to be split, the portion of the sample not used for the determination of barbiturate at the local laboratory was to be frozen and sent to the National Institutes of Health for comprehensive analysis for all of the drugs then known to produce flattening of the EEG. This second independent analysis of the same sample was to provide quality control on the local blood barbiturate determinations but in addition was designed as a much more comprehensive analysis to see if local barbiturate screening alone were adequate for routine use in brain death suspects.

RESULTS OF THE NINDS COLLABORATIVE STUDY

Demography.--As previously indicated the entrance criteria to the study were profound coma and apnea. Five hundred and three patients who were the subjects of the published reports of that study met these entrance criteria, at least once. Two patients who initially met the criteria recovered spontaneous respiration only to be re-entered into the study later. Therefore, 503 instances of coma and apnea were recorded in 501 individuals. Another 315 patients were screened by the study investigators but were not entered into the study because they failed to meet one or the other of the two major criteria. The patients were accessioned to the study independent of the etiology of their coma and therefore among the 503 instances there were multiple instances of drug intoxication and other etiologies in which primary pathology was not a destructive lesion in the central nervous system.

The demography of the patient base and the etiology of coma have been published in several references and in diverse formats (76,81,82). In general there are two peaks in the distribution of patients by age: one in the second decade corresponding with the high incidence of cerebral trauma in the younger age groups, the other in the sixth decade due to the high incidence of cardiac disease overlapping with the younger age groups subject to strokes. There were a few children under age 10, the most common diagnosis being cerebral trauma. There were 275 males compared to 222 females. There was a significant subpopulation of patients, 105, with coma due primarily to cardiac arrest followed by cardiopulmonary resuscitation (5).

Perhaps because the patients were not selected for etiological diagnosis, there was a wide variety of latencies in the patient population from onset of the primary insult to cerebral unresponsiveness (coma) and insult to apnea. The majority of patients (333) lapsed into coma within two hours. In most cases, coma preceded apnea by 2-16 hours (82).

Thirty-four patients developed coma 16 hours to 2 days after cerebral insult; another 58 patients in the study lapsed only after more than 2 days. Thirty-three patients had unknown intervals from the onset of their illness to the accession to the study.

In cases of ingestion of depressant drugs by persons living alone, the only measurable time period was from the time of discovery of the comatose patient to the time of apnea or to the time of accession to the study. Much of the slippage between coma and apnea may be due to the variety of diseases under consideration, including slowly progressive diseases such as infections and endogenous intoxications along with those of instantaneous onset such as trauma and cardiac arrest.

A variety of relationships have been reported by Walker (82) between treatments given, both pharmacological and surgical, none of which seemed to correlate with outcome.

Of the total patients accessioned, 345 died of spontaneous cardiac arrest while the respirator continued in effect. Another 114 patients were pronounced dead by their physicians, using variable sets of criteria (uncontrolled within the study) for the pronouncement of brain death and then had their respirators stopped.

Another 44 patients recovered (4,6). Twenty-four of the survivors were patients who were known during their hospital course to be the victims of drug overdose. Among the survivors were a few each of patients with primary cardiac disease and cerebral trauma and isolated incidences in several other disease categories. Only 26 of the 44 survivors were free from deficits three months after accession to the study.

Neuropathological Findings.--As soon as the first patients who died in the study came to autopsy it became apparent that there was less than unanimity among investigative and consulting pathologists reviewing material on the criteria for total destruction of the brain. Whether the complete picture of the "respirator brain" was required and what criteria constituted the "complete picture" of that entity were controversial. Early on in the reduction of data, not all pathologists agreed upon what a respirator brain was, when one was present or absent; occasionally pathologists thought that some part or parts of a given specimen showed changes characteristic of the respirator brain while othere did not; therefore there was a "partial" respirator brain encountered in some specimens and not all consultants on review panels charged with resolution of controversial interpretations and ambiguous changes could agree among themselves as to the criteria for respirator brain. Although it may have been presumed that "respirator brain" was a well defined entity which suggested death of the brain prior to termination of the respirator, a review of the literature once again revealed discrepancies of opinion among experts in the field of neuropathology on the criteria for a respirator brain, for autolytic changes which occur post mortem, and indeed whether or not there be any pathological change pathognomonic of death of nerve cells (1,24,36,46,47,51,52,76).

Indeed, from the specimens generated within the study it seemed that while there was generally good concurrence between unresponsive coma, apnea, absence of cephalic reflexes and electrocerebral silence with changes generally considered characteristic of the respirator brain, a few specimens even early in the study showed none of the pathological evidence of respirator brain despite electrocerebral silence up to the moment of spontaneous cardiac arrest; a few others showed changes of the respirator brain despite continuous biological activity in the EEG until the moment of death. These discrepancies are described in detail in the reports by Walker (82,84) and Walker and associates (76). Even when corrected for time on respirator concordance between the respirator brain and *in vivo* recordings of physical findings and EEG's is far from perfect.

Once the dissociation between EEG data, clinical criteria for brain death and pathological changes at autopsy became known, it was impossible to accomplish the objectives of the collaborative study described in the above Critique of Study Design. From the pilot study as executed it was not possible to verify that a diagnosis made prior to cardiac arrest by any set or subset of criteria would invariably correlate with a diffusely destroyed brain. Nonetheless, the clinical criteria linked with EEG findings did predict death within seven days (81).

Of the 459 patients who died, 240 had autopsies, in 10 cases the brain was not removed and in another 4 the brain was not available for analysis. Therefore, there were 226 brain specimens available for meticulous neuropathological analysis. The details of that analysis are reported elsewhere (76). No more than 40 percent of these specimens were diagnosed as respirator brains, independent of time on respirator or etiological diagnosis (82,84).

In distinction to the interpretation by Black (11,12) that "the collaborative study group tried to establish the respirator brain entity in two ways: by an opinion poll and by examination of many brains and spinal cords in their study." The opinion poll was launched retrospectively only after the study failed to produce consistent correlations between respirator brains and clinical criteria.

Nonetheless a survey of the membership of the American Association of Neuropathologists was undertaken during the data analysis phase (i.e. in retrospect), the results of which were subsequently published (47).

EEG Findings.--A major publication, An Atlas of Electroencephalography in Coma and Cerebral Death was generated from the data in the collaborative study (8). Several papers on the subject of the EEG changes, their limitations, and the evolution of certain patterns, progressive changes, during the dying process have been published by Bennett (9) and by Hughes (26,27). Also consensus among American physicians and participants in the study was summarized by Dr. Eli Goldensohn (21) that the EEG is a highly valuable tool in determination of brain death and that where available, should be used:

"If cerebral activity is seen on the EEG an individual cannot be considered brain dead, and that a properly run and interpreted EEG... has a probability of correctness that matches the expert clinical neurological examination."

However, although the flat EEG did not always coincide with total brain destruction, it did predict a fatal outcome in all but two cases of drug intoxication.

CNS Depressant Drugs.—The problem introduced by the presence of drugs in the blood has also been reported (78,80,82).

To briefly review the drug dilemma, 36 patients were admitted to the study in coma and apnea with a clinical diagnosis of intoxication made either because of a suicide note or a found empty bottle of pills. As a result of the diagnostic workup, including barbiturate blood levels drawn at the clinical center hospitals, the number of cases in which drugs were involved grew to 61.

Despite the requirement of the protocol, of the 503 patients who were comatose and apneic, only 313 ever had blood levels reported for data and analysis. This may have been due to oversight, the emergency care and the obviousness of the primary diagnosis detracting from the importance of this detail in the research protocol, or may be due to short survival time after accession to the study. Nonetheless, of the samples sent to the central laboratory at NIH, 87 were found to have either barbiturate or nonbarbiturate sedatives in the blood which could suppress the EEG. Therefore, 26 patients (87-61=26) of a subtotal sample 313 were found to have CNS depressants in their blood which were not suspected clinically at any time during the workup and care at the centers and therefore were not known prior to death or termination of resuscitation.

Since only 36 patients had an admission diagnosis of drug intoxication, the other 25 patients found at clinical centers must have had a secondary diagnosis of drug intoxication, since each had an acceptable etiologic diagnosis before barbiturates were discovered.

Finding small amounts of drug in the blood may be significant since the amount of drug in the blood rarely correlated with severity of coma even in primary suicidal attempts. Quantitative levels were usually no greater than the recommended therapeutic range for the drug (80,82). This discrepancy was probably due to delays in the sampling of the blood after the onset of coma; the interval from ingestion of drug to discovery of the victim was uncontrolled, while the interval from discovery to treatment was prompt and measurable.

When coupled with alcohol there were 51 patients with nervous system depressants in whom there was some other obvious cause of coma. Presumably the priority for drawing a routine test for purposes of the study was relatively low in those cases of obvious closed or open head injury, and therefore some additional samples may have been missed in rapidly fatal cases. Drawing of the blood sample may have been delayed until after the initial pharmacological treatment associated seizures or some other condition requiring the use of analgesics, sedatives or tranquilizers. Such drugs were used therapeutically at some point in the clinical course of 150 of the 503 patients.

Whether the drug was taken intentionally or accidentally by the patient, or given iatrogenically, drugs known to depress the EEG and respiration may contribute to the overall picture of coma, apnea and/or electrocerebral silence, even as reduced cerebral blood flow. Therefore their presence must be known whenever pronouncement of death is being considered. This is even more important since not only is hypothermia (50,73) reputed to have a protective effect on the brain during cardiac arrest, but so also may anesthesia (36); a variety of barbiturate agents in various clinical and experimental situations are thought to lower brain metabolic requirements, reduce reactive vasogenic edema, or both (68); by either of these mechanisms these drugs are reputed to afford a modicum of protection. Theoretically, the very drug producing coma and apnea could prolong the period of tolerance of apnea. Therefore, the presence of CNS depressant drugs, even qualitatively detected in the blood subverts the confident diagnosis of diffuse brain necrosis or the prognosis of hopelessness.

Neurological Signs in Brain Death.--Correlations have been made between the clinical findings, EEG and neuropathological findings by Allen et al. (5), and Walker (76,78,82). From a large subsample analysis, Allen and his associates reduce the number of reflexes necessary to exclude the presence or absence of brain stem function to a few highly reliable reflexes of statistically high predictive value in relation to a morphologically "dead brain". The pupillary reflex to light, vestibular reflex to caloric stimulation of the external canal, the oculocephalic reflex and the corneal reflex were shown to be more highly predictive of death than were pupillary size, jaw jerk, audiocular, snout reflex, cough reflex. Walker's analysis of the entire sample (82) rates absent pupillary reflex to light as having the highest statistical correlation with outcome, exceeding the correlation coefficient even for all cephalic reflexes combined. Thereafter his data roughly parallel those of Allen, in that corneal, vestibular and oculocephalic reflexes are more predictive of outcome than cough, swallowing, jaw jerk, snout and pharyngeal responses. Walker also points out, however, that in the 503 patients studied, swallowing, pharyngeal, cough and vestibular reflexes were frequently omitted from the examination (82). This may have been due in part to the logistical and technical problems encountered in patients with extensive head dressings, occluded external auditory canals, and endotracheal tubes in place.

Both agree that patients frequently met all usual criteria for brain death while the spinal reflexes were still active.

DISPOSITION OF PILOT PHASE FINDINGS

The collaborative study found that of 503 comatose, apneic patients, 187 also had electrocortical silence in their EEG. All but two of these patients died; both survivors were drug intoxicated patients (81). Thus, three basic criteria of cerebral unresponsivity, apnea, and ECS have a 99 percent accuracy in predicting death within one week; however, the study did not distinguish clearly between brain death and irreversible coma. If the target of the study were simply the prediction of a fatal outcome, then any additional tests, clinical electrophysiological, biochemical, or radiological would be for the purpose of improvement upon the 99 percent accuracy of the three basic criteria.

If the target of the study was the identification of totally destroyed brains, the failures of some cases meeting clinical criteria to correlate with pathological evidence of the "respirator brain" may have been due in part to uncontrollable variables in the rate of evolution of the various criteria over time, reflecting variables in slow versus rapid pathogenesis of the brain disease.

In setting up this collaborative study or any hospital-based study, it is impossible to control the variable latency between the onset of the primary disease or ictus and time of arrival at the hospital. There was also variation in the time from admission to the hospital to the time patients met criteria for accession to the study. While these variations may account for some dissociations among EEG findings, neurological signs, and pathology, and between blood levels quantitatively determined and the depth of coma caused by drug ingestion, etc., at the time the study was done, it usually required approximately 7 or more hours for completion of the routine diagnostic studies and the initiation of appropriate therapy for the primary diagnosis. Therefore, the collaborative group recommended that a minimum of 6 hours transpire between the onset of coma and apnea and the application of criteria for brain death. Most of that interval would be consumed in the ordinary diagnostic workup (81).

Although the pilot study group recommended bolus transit curves as confirmatory sign of the absence of cerebral circulation, and even suggested a potential use for echoencephalography (74) and other indirect measures of cerebral circulation in the same way (77), the investigators recognized that not enough studies of cerebral blood flow, either by direct contrast angiography or by bolus transit curves or echoencephalography were performed within the study to have statistical significance. Nonetheless it was thought that if death were to be pronounced in the shortest possible interval after the onset of coma, some confirmatory test for the presence or absence of cerebral circulation be superimposed on the basic predictive criteria, of coma, apnea and ECS to ensure total brain destruction. Since neither cerebral bolus transit curves nor echoencephalography had been validated for reliability and reproducibility against cerebral angiography, it was controversial at the time as to whether the recommended criteria should be put to use in a definitive study in search of a statistical conclusion.

It was decided after review of the ad hoc advisory committee not to seek a statistical conclusion since exceptions had already been found, but rather to validate the preliminary reports of utility of bolus transit curves (14,16) and radionuclide angiography (40).

DEVELOPMENTS SINCE THE NINDS COLLABORATIVE STUDY OF BRAIN DEATH

In the late phases of data analysis during the NINDS study, because of the controversy and uncertainty over the minimum prerequisites for the diagnosis of a respirator brain, a questionnaire was distributed to the enrolled membership of the American Association of Neuropathologists. While the study was not designed to demonstrate or define respirator brain by consensus or democratic poll, the survey did demonstrate the limitations in understanding of the morphological criteria for death among the membership of that organization. Although some did not use the term respirator brain, a majority did and thought the changes were due to some time dependant pathological process. Ninety-five percent of the respondents agreed that there was little or no inflammatory cell reaction as compared to the amount of tissue necrosis. This is not surprising since the absence of an inflammatory response to injury of any kind is a standard principle of forensic pathology suggesting post-mortem change.

From the NINDS study, it is suggested that the "respirator brain" probably takes approximately 12-24 hours to develop (76,82). Signs of neuronal damage, such as "red neurons" may appear sooner, but the question of reversibility of such changes has yet to be established. Some attractive theories have been proposed by Walker (82) and others (37) on the pathogenesis of the respirator brain, while others reject the concept completely maintaining most of the features to be post-mortem changes (1). Perhaps recent experimental models of "brain death" may help distinguish pathological post-mortem components of totally destroyed brains (38).

Since the completion of the NINDS collaborative study on brain death there has been increasing acceptance and general use throughout Europe of four vessel aortocranial angiography to establish the absence of cerebral circulation as confirmation of brain death. This criterion is most attractive because of the minimum time required in determining total brain destruction (two injections of contrast medium, 25 minutes apart).

Since the American study merely indicates that individuals with unresponsive coma, apnea and ECS by electroencephalography, in the absence of drugs, have no likelihood of recovery and in fact will die within 7 days, confirmation by the independently tested parameter of cerebral circulation showing no passage of blood in or out of the brain would still be required to prove total destruction of the brain. Furthermore several independently determined variables, namely neurological examination, EEG, and cerebral blood flow, may be expected to cross-correlate and thereby cross-validate each other in patients whose brains have permanently stopped functioning and are destroyed; when all three converge at a point in time, all indicating a non-functioning, destroyed brain, the chances of error in the diagnosis of brain death are virtually nil (81). Despite the simplicity and attractiveness of this construct of brain death, these criteria could only be applied retrospectively to 17 of 503 patients in the American (NINDS) study (77,81). This is the total number of angiograms (not all of which were four vessel studies) that were performed in the study.

The reason for reticence to perform angiograms on these patients is not greater availability of angiography suites throughout Scandinavia, but probably the social-medical systems operant in these countries respectively. Physicians in this country would be loathe to seemingly jeopardize their patients' slim chance for recovery by doing an invasive diagnostic study which bears with it a morbidity and indeed a "mortality" rate in such moribund patients. Cardiac standstill during or immediately after angiography might introduce the legal question of liability.

The reliability of bolus transit curves, according to recent reports by Korein, Braunstein and associates (31,34,35) compare favorably with four vessel aortocranial angiography; they found that independently determined clinical neurological findings, electroencephalographic findings, and bolus transit curves permit accurate diagnoses of brain death, and in collaboration with Pearson, (51,52) have established excellent correlation of these parameters with pathological criteria of a destroyed brain.

Braunstein et al. (17) have reconciled their isotope bolus curves with known quantitative flow data suggesting the threshold for continued cerebral viability at from 20-22 percent of normal. Allowing for a contribution to this figure by extracranial sources and based upon their own validation studies using four vessel aortocranial angiography, they conclude that flows of up to 20 percent of normal correspond to their "intermediate" curves, and these in turn correlate with mainly unmasked extracranial blood flows.

Braunstein argues that since maximum duration of tolerance of such remarkably reduced flows is 20 minutes, his group, as do the Scandinavians, think that a repeat isotope transit curve is necessary. They suggest that a one-hour interval provides a comfortable margin of safety to insure certainty with little loss of time (17). [The Scandinavian criteria using contrast angiography suggest a second injection twenty-five minutes later (28).]

Those who advocate this relatively simple, portable method for assessment of cerebral circulation further stipulate that any potential error inherent in that method, used along with clinical criteria of unresponsive coma, apnea, absent cephalic reflexes and electrocerebral silence, would permit the dead patient to be misdiagnosed as "alive." Only false positive flows suggesting cerebral circulation can be caused by extracranial contamination; falsely flat, no flow, studies cannot. Such an error would be permissible, since the worst consequence could be some delay in pronouncement of death and removal of organs (17).

The collaborative investigators concurred in the use of some measurement of cerebral circulation as a confirmatory test in cases in which extensive head trauma, therapeutic devices, or procedures preclude testing of all cephalic reflexes, or when in doubt remained after completion of all tests for minimal criteria, yet an early diagnosis of brain death is desired (82). Used in this way, no statement was made as to a need to repeat the "confirmatory test" of cerebral blood flow. Since the determination of blood flow would be derived independently from either clinical or EEG findings, the overlap of criteria reflecting the same biological process would reduce the chance of human error and uncertainties introduced by drugs in the blood to "infinitesimal" proportions. The criteria reported were recommended for field trial in order to work out indications for blood flow studies and resolve logistical and statistical problems. These recommendations were formulated prior to the reports of further validating studies and methodologies recommended by Korein, Braunstein, Pearson and their collaborators (17,31,51). Specifically the repetition of a blood flow curve after one hour recommended by the latter investigators, while more conservative, seems to remove all doubt about total brain destruction when serial tests indicate no blood reaching the brain over that length of time. If isotope bolus curves could miss small amounts of blood flow to the brain, then even repeat tests might not be definitive in cases of barbiturate intoxication or hypothermia, either of which might lower the cerebral blood flow through autoregulation, i.e. by lowering metabolic demand, or by prolonging in some other way the time interval over which the brain could tolerate ischemia without total destruction.

Since the report of the American study, the Conference of the Royal Colleges and Faculties of the United Kingdom recommended a set of criteria which excluded the use of the EEG (18). The criteria also required that patients be suffering from a known destructive brain lesion, thereby eliminating the problem of intoxication as a potential cause of brain death. The recommendation was that in patients meeting the criteria, support may be withdrawn.

In several cases reported within the collaborative study, by Walker (81,82) and by Allen (6), pontine hemorrhages or infarcts may completely remove the brain stem reflexes and respiration while the cerebral hemispheres remain structurally intact. Those cerebral hemispheres, having an independent source of circulation, could continue to produce electrical activity by the EEG. While such cases usually die, cases of survival are also known. Although such patients might fall into the category of prolonged vegetative states, they are not "brain dead ." Such patients with EEG activity would be called "brain dead" by the British criteria.

While the prognosis for recovery of function is nil and the probability of death within days to weeks is extremely high, one major question remains and perhaps has been brought into focus by the NINDS

Collaborative Study. That question is: does a fatal prognosis permit the physician to pronounce death? It is highly doubtful whether such glib euphemisms as "he's practically dead,"...."he can't survive,"....
"he has no chance of recovery anyway," will ever be acceptable legally or morally as a pronouncement that death has occurred.

This is more than a mere semantic distinction. A physician must pronounce that death *has occurred* before he can either perform an autopsy or remove the "cadaver" organs for transplantation to another human being. In the planning days of the NINDS Collaborative Study of Brain Death, and even now, physicians and society feel comfortable with the humanistic sentiments of reducing unnecessary suffering by the patient and relieving financial and emotional drain on the family caused by an unduly prolonged terminal illness. The idea of withdrawal of artificial support methods to permit death to occur is relatively old, morally defensible, and hardly controversial when done in keeping with the wishes of the family or when the desires of the patient himself have been previously made known. It may not be necessary to pronounce death *before* support is weaned. This was the concept concurred in by Pope Pius XII (54).

When organ transplantation is contemplated, the donor must be dead first. *That* death must be just as definitive as it would be if respiratory support were not involved. Because of large interhospital and interstate commerce in viable organs, matching pre-tissue-typed recipients with potential donors, frequently tissue-typed during life, the respirator is *not stopped* when death of a donor is pronounced *but* resuscitative efforts are continued to support the desired organs. The "resuscitory effort" will be continued until after the removal of the desired organs, a situation which permits no tolerance for error. Any risk of error must favor calling the dead patient alive. Thus when organ donation is contemplated, there can be no risk of pronouncing the live brain dead whereas in the instance of withdrawing artificial support in a situation of hopelessness, death, the natural consequence of termination of artificial support may occur moments or even hours after withdrawal of resuscitory devices. The criteria recommended by the Royal Colleges which exclude the EEG may be adequate to withdraw support (18), but are they adequate to maintain support pending removal of organs? Perhaps the transplantation programs are not as vigorous in England as in the United States.

A development of startling proportions occurred concurrently with the conclusion of the pilot phase of the collaborative study of brain death. The first computerized axial tomographic (CAT) scanners were applied to neurological diseases. In the interval since the conclusion of the study and the present, it has become standard practice to obtain computer-assisted tomograms of the head in comatose patients presenting at American hospitals having such equipment. Such studies are often obtained en route from the Emergency Room to the Intensive Care Unit. While the capability of this technology to reduce the latency inherent in pronouncement of brain death has barely begun (56), initial CAT scans promptly segregate brain death suspects into those with a structural lesion of the brain and those without a detectable lesion early in the course of coma. The net effect upon physicians in centers having CAT scanners and renal transplantation programs has been to eliminate the 6-7 hours previously required to establish the diagnosis in many cases, particularly in massive brain hemorrhages. Neurologists are often requested to pronounce death or establish a prognosis based upon clinical and CAT scan data alone within an hour or two after the onset of coma. Even if isotope bolus curves may indicate absence of cerebral circulation within an additional few minutes at an appropriately equipped center, it seems exceedingly difficult to both announce the death to the bereaved next of kin and promptly request permission for removal of organs before terminating the respirator, especially if the deceased was last seen alive and well by his loved one an hour or two before the confrontation in an emergency room. In such situations both the physicians making the judgement that death has occurred and requesting removal of organs are frequently strangers to the family.

In many such instances, the earliest possible pronouncement of death may be incompatible with obtaining permission for removal of vital organs, except in the rare instances in which the preferences of the suddenly deceased had been made explicitly known to the family before the catastrophe. For practical purposes such haste adds little to the confidence of the family in granting or denying permission, and may increase the risk of error by physicians.

While the CAT scans permit accurate information on the nature and extent of acute brain lesions, in practical terms they cannot be used as a substitute for screening for depressant drugs, cerebral circulation studies, or a doctor-patient relationship. Therefore, ready availability of CAT scans at organ procurement centers does little to reduce the 6-hour interval recommended by the collaborative investigators.

When organ transplantation is contemplated it is desirable to maintain the organs in as fresh a state as possible and a prolonged sequence of examinations repeated over time risks the biological integrity of the allograft. Multiple independently determined parameters that can be shown to indicate nonfunctioning and total destruction of the brain over the shortest interval of time offer the maximum certainty with the least risk of error. In cases where organ donation is not contemplated and doubt exists, or in instances where four vessel angiography, radioisotope bolus transit curves, etc., are not available, or where drugs are thought to contaminate the picture and perhaps play a role in the electrocortical silence or apnea, one can always wait for 24 or even 48 hours (69). When one cannot wait, comatose apneic patients may be shown to have a nonfunctioning brain by the absence of cephalic reflexes and no biological activity in the EEG. An independent determination of cerebral circulation will offer evidence that the nonfunctioning brain is totally destroyed and the patient, therefore, is dead.

SUMMARY

The collaborative study of brain death was planned and designed as a nonintervention pilot project investigating the feasibility of a fixed protocol study at multiple clinical centers. The project was undertaken with a sense of urgency engendered by public, legislative, and juridical concerns of the definition of death generated by the notoriety given human organ transplantation.

The study done was a prospective test of whether criteria suggested by the ad hoc committee of the Harvard Medical School, or a subset of those criteria would correlate with autopsy proof of total brain destruction or the respirator brain.

While the survey readily identified deep unresponsive coma, apnea, absent cephalic reflexes and a single flat EEG in the absence of drugs as reliable predictors of death within 7 days, it was also found the autopsy data could neither prove nor disprove the accuracy of the clinical diagnosis in an uncontrolled study. While irreversible coma was easily identified, a "dead brain" could not be, using clinical signs and EEG criteria alone.

Nonetheless, valuable observations were made on the accuracy, reliability, practicality and limitations of several parameters previously recommended for use as indicators of brain death.

Methods in common clinical use for detection of drugs in the blood stream could not identify all the drugs encountered by comprehensive screening; neither could quantitative analysis of the blood distinguish primary drug intoxications as the cause of coma from incidental contaminants.

The utility and pitfalls of the EEG as the major confirmatory test for death in comatose apneic patients were evaluated and reported in a monograph.

In an ancillary project at one collaborating center, radioisotope bolus curves were developed and subsequently have been validated as indicators of the presence or absence of circulation to the brain parenchyma.

Although the NINDS collaborative study did not produce a new definition of brain death, it did show that a fatal prognosis or irreversibility could be established within six to seven hours of onset of coma.

Whether irreversible coma and brain death were one and the same entity was not established at the time the study was planned nor was that issue directly addressed in the collaborative study design.

Subsequent scientific developments and public opinion influenced by the outcome of certain celebrated court decisions permit the interpretation that they are not the same.

Therefore the criteria for the diagnosis of irreversible coma may not require confirmatory tests of electrophysiological brain activity (EEG) or cerebral circulation, but prompt pronouncement of death by criteria for total brain destruction may require both.

EPILOGUE

The use of the term "brain death" is awkward because it uses the noun "brain" as an adjective. On the other hand, etymological purists interpret "cerebral" as the adjective derived from the Latin word "cerebrum." Cerebrum in scientific English is used to indicate the contents of the cranial cavity above the level of the tentorium cerebelli and excludes the brain stem and cerebellum. Some scientists and philosophers distinguish among "brain" death, "cerebral" death, and "cortical" death.

Modifiers of "death" suggest there may be more than one kind of death. Perhaps the best way to avoid such confusion of terms as used by jurists, doctors and as understood by the public is to allow that there is only one "death," and that death occurs when the brain "dies." If the heart stops and is not resuscitated, there will be total destruction of the brain within a very few minutes. Although other vital processes may continue, including certain biochemical and enzymatic activities characteristic of living cells, the physician does not wait until the body temperature cools and the finger nails stop growing to pronounce the patient dead. In situations very commonly encountered in modern hospitals, in which the brain stops functioning permanently, completely destroyed before the cardiorespiratory system ceases its function, death may still be pronounced. Perhaps the preferred nomenclature should be that death may be pronounced by either "cardiorespiratory criteria" or by "neurological criteria" rather than refer to cardiac death, brain death, or cerebral death.

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NEUROPATHOLOGICAL FINDINGS IN THE BRAINS OF PATIENTS ADMITTED TO THE COLLABORATIVE STUDY

by

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INTRODUCTION

An account of the neuropathological findings of the material derived from the Collaborative Study on Cerebral Survival has already been published (34). This chapter will summarize the results of that study and discuss some of the problems related to the pathological substrate of cerebral death.

METHODOLOGY

All patients admitted in or developing a comatose and apneic state in nine participating hospitals in the United States were the subjects of a collaborative study (table 1). These patients after resuscitative procedures were initiated were maintained on a respirator while physical and neurological examinations, electroencephalograms, blood studies for cytology, electrolytes, and drugs were made. Appropriate therapy as prescribed by the attending physician was administered (3).

Four hundred and fifty-nine of the 503 persons admitted to the study had cardiac arrest, 345 while on the respirator and 114 after mechanical ventilation was stopped. The time of the ventilator varied from less than 1 hour to more than 28 days (table 2). Only 240 of the 459 deceased persons (52.3 percent) had a postmortem examination; 226 brains were examined (table 3). A protocol provided an outline for a standardized neuropathological workup of these brains.

Methods of Neuropathological Study.--Both brain and spinal cord were removed, unless permission limited the examination. A description of the dura mater and its sinuses, and of the external appearance of the brain was recorded. Before the brain was sectioned, color transparencies were made of its base and convexity, and after sectioning the brain, four representative sections were photographed. The brain was fixed in 10 percent buffered formalin for one to four weeks, then cut and blocks taken for paraffin embedding and staining from:

1. Lumbar spinal cord enlargement
2. Mid-thoracic region
3. Upper cervical spinal cord
4. Medulla at the level of the obex
5. Pons at the exit of the trigeminal nerve
6. Mesencephalon
7. Coronal section of the cerebellum to include part of the anterior lobe and vermis as well as the hemisphere

8. Thalamus and hypothalamus at the level of the mamillary bodies
9. Coronal block of the mid-frontal lobe along the midline to include the watershed areas
10. Coronal block across the central sulcus
11. Coronal block of the medial occipital lobe across the calcarine fissure
12. Coronal sections of the medial temporal structures to include the hippocampus.

These sections were stained with hematoxylin and eosin, Luxol fast blue, and periodic acid-Schiff (PAS).

The neuropathologist at each center prepared a narrative and coded report on all cases. The material was subsequently reviewed by the project coordinator who referred those cases of particular or controversial interest, either from the standpoint of the neuropathological diagnosis or the presence of a respirator brain, to a panel of neuropathological consultants. A few representative cases were included so that the consultants might become aware of the types of cases which were being studied. Although notes were made of the consultants' opinions, the coding of the neuropathology checksheets, unless otherwise stated, was that of the local neuropathologist. In general, neuropathological diagnoses entertained by the local pathologist and the members of the consultant panel were in essential agreement, although the interpretation of the findings, particularly in reference to the diagnosis of the respirator brain, was less consistent.

GENERAL NEUROPATHOLOGICAL FINDINGS

The postmortem examinations were made on the average of 15.3 hours after death. There was less delay in performing the autopsy on individuals on whom resuscitative measures were stopped than on patients having a cardiac death. However, the difference, approximately two hours, probably played no role in the condition of the brain. In this series, the sagittal or transverse sinuses were clotted in 14 percent of the cases, and in more than half of the autopsies, the sinus walls were normal both in those patients having cardiac death and in those having resuscitation stopped.

The mean weight of the brains examined was 1450 ± 196 grams (range 900-1800 grams), a figure within the range of a series matched for age and sex. However, those cases succumbing to cardiac arrest had lighter brains than the brains of individuals whose resuscitative measures were stopped on the basis presumably of cerebral death.

Average weight of brain (N = 194)	1,450 ± 196 gm
Average weight of brain of patients with cardiac death (N = 139)	1,430 ± 198 gm*
Average weight of brain of patients with cerebral death (resuscitation discontinued) (N = 55)	1,500 ± 180 gm*

*p - .014

Since the sex distribution was the same in the two groups, the difference in weight may be due to the factor of age or to the time on the respirator. Individuals having a cardiac death were on the average about 10 years older than those on whom resuscitation was stopped (48.6 vs 36.1 years). However, in middle life, age related differences in brain weight are minimal, so that the disparity in brain weight is probably not related to age. Most patients diagnosed as cerebral death had resuscitation stopped after 1 or 2 days, whereas, many of the other patients were artificially aerated for longer periods of time. Since the weight of the brain gradually increases during the first 24 hours after the beginning of resuscitative measures (17), it is possible that the longer period of time on the respirator was responsible for the heavier brains of the cerebrally dead.

Appearance of the Brain.--In this series, approximately 10 percent of the brains appeared grossly normal. The surfaces of most of the brains were congested and yellow; the convolutions were broadened and flat and the sulci were narrowed or mere slits. In spite of fixation, the brain felt soft. In about one-half of the cases, the primary lesion was prominent, but specific reference will not be made to this pathological state. The most common secondary effects that gave rise to elevated intracranial pressure--swelling and congestion--were present in more than one-half of the brains, usually both in cerebellum and cerebral hemispheres. Occasionally the swelling was confined to the supratentorial structures; such hemispheral edema with normal brainstem and cerebellum occurred in 21 cases. More commonly, the edematous and necrotic cerebellum displaced the posterior fossa contents so that the tonsils herniated into the occipital foramen and along the upper cervical spinal cord. Caudal herniations at the tentorial notch were commonly found in the brains of patients who had been on the respirator for 24 hours or more; in all they occurred in 60 percent of cases.

On sectioning the brain, the ventricles were small or slit-like, and often distorted or displaced by the primary lesions. The demarcation of gray and white matter both in the cortex and basal regions was less pronounced than usually seen.

PATHOLOGICAL ALTERATIONS

Spinal Cord.--In this series, 76 of the 127 cases in which the spinal cord was examined were reported to be grossly normal. Microscopically, in many cases, the substance of the spinal cord appeared normal. However, in about one-third of the cases, pathological alterations such as edema (13.8 percent), petechial hemorrhages (5.7 percent), neurolysis of anterior horn cells (11.4 percent) were noted (figure 1B). One of the more spectacular phenomena--displacement and lodgment of cerebellar fragments in the spinal subarachnoid space was found in approximately 10 percent of the cords examined. The necrotic cerebellar fragments along the cord were composed of folia in various stages of disintegration. Histologically, the granular cells of these folia were most severely affected and the Purkinje cell layer was edematous and its neurons often fragmented or swollen, with poorly staining cytoplasm. No inflammatory reaction was noted at the site of these folial deposits (figure 1A).

At the cervico-medullary junction, where the blood supply may be derived from either vertebral or spinal arteries, myelopathy in the form of localized edema, necrosis, infarction, or hemorrhage, was present in 54 cases. These changes were associated with varied lesions in other parts of the brain in 36 cases. In an additional 17 cases, acute and chronic neuronal changes were seen on microscopic examination of the upper cervical cord (figure 2A).

Brainstem.--The medulla, pons, and mesencephalon were common sites of pathological changes related to both the primary disturbance (tumor, vascular insult) and to alterations secondary to the death of the brain. In this series, only about 15 percent of the cases appeared to have a normal brainstem. The medulla oblongata was flattened and edematous in about half of the cases, the pons was swollen, and/or macerated especially on its periphery. The mesencephalon, edematous, compressed and distorted, often had midline or periaqueductal flame-shaped hemorrhages especially if transtentorial herniations were present (figure 1B). On microscopic examination, interstitial spaces were seen both about the neurons and the small blood vessels. The axons and their myelin were often preserved. The nerve cells were diminished or absent in some nuclei such as the inferior olivary nucleus, and those preserved had a homogeneous eosinophilic cytoplasm and poorly defined nuclear structure (red neurons) (figure 3).

Cerebellum.--In this series, 39 cases had no gross abnormality in the cerebellum. In 117 brains, the cerebellum was swollen, and the necrotic and discolored cerebellar tonsils were herniated into the foramen magnum. Occasionally, the swollen cerebellum pushed its anterior lobes into the incisura with a consequent herniation and necrosis of the culmen. On sectioning the cerebellum, the narrowed folia had a grayish white, almost silvery, appearance which is characteristic of lysis of the granular layer. Histologically, the most prominent changes were severe lysis of the granular layer associated with varying degrees of neurolysis of the Purkinje cells in about one-third of the cases. Usually, the junction between molecular and granular layers was edematous and necrotic with a loss of many Purkinje cells. In other cases, the granular layer was necrotic but the Purkinje cells were relatively preserved. Again, the granular cells were little attenuated but the Purkinje cells showed lytic changes. The molecular layer was rarely if ever severely involved. The pia arachnoid was preserved although its blood vessels were congested (figure 4).

Diencephalon.--The diencephalon was damaged to some extent in almost 85 percent of the cases. The most common lesion was necrosis and edema but small hemorrhages and infarctions were studded in areas containing relatively normal cells particularly in the hypothalamic or periventricular regions.

Cortex.--The cerebral cortex was the most severely damaged portion of the brain. Only about 6 percent of the cases in this series had no gross cortical lesion.

The type and degree of pathological alteration varied from case to case. In a few brains, the changes were minimal.

Depending upon the type of the primary etiological condition and its duration before circulation ceased, various reactions to the lesion were apparent. However, the following nonspecific changes were seen to some degree in almost all cases. Except for the outer layers, in most cases, the cerebral cortex was punctate with clear spaces about the neurons and capillaries. Many neurons had a homogeneous cytoplasm with an eccentric nucleus containing granular nucleoplasm and an indiscernable nucleolus. The nuclear membrane was often indistinct or fragmented. The glial cells of the cortex seemed to be less involved and their morphology was fairly well preserved. However, in severe cases, with marked edema and necrosis, the typical swelling of the oligodendroglia and the classmatodendrosis of astrocytes was seen. But even under these circumstances, there was no small round cell infiltration nor microglial proliferation. Usually, in hemorrhagic areas, hemosiderin particles were not found within gitter cells or neurons.

The pia arachnoid was usually well preserved although the cell nuclei stained darkly. The capillaries of the cortex, often partially collapsed and surrounded by a clear perivascular space, had normal appearing endothelial cells. The myelinated fibers entering the lower cortical layers were edematous but the axons appeared to be preserved. In the underlying U fibers and white matter, the oligodendroglia and astrocytes usually were relatively preserved; in places the astrocytes showed clasmatodendrosis but the oligodendroglia had little swelling. However, in severe cases, the entire cortex was necrotic with only a few glial endothelial cells staining (figure 5).

The ventricular ependyma was usually well preserved, although in some cases the cells were swollen. The cells of the choroid plexus had a homogeneous swelling but the gross structure of the plexus remained (figure 6).

In spite of the necrosis and autolysis there was no evidence of inflammatory reaction--no perivascular infiltrations, no phagocytosis or microglial proliferation and rarely astrocytic swelling and hyalinization. When the latter changes were present, the primary condition had existed for several days before clinical evidence of cerebral death.

Pituitary Alterations.--In this series, the pituitary gland was not consistently examined, so that the frequency and type of pituitary pathology cannot be estimated.

DISCUSSION

The pathological substrate of a dead brain, it might be assumed, would be a readily recognizable morbid entity. In their first case, Bertrand et al. (4) were impressed by the marked edema, softening and necrosis, especially pronounced in the gray matter, and severe neuronal alterations without inflammatory reaction or vascular thrombosis. Adams and Jéquier (2) described a variable degree of pannecrotic encephalopathy as the pathological basis of cerebral death. Kramer (21), Lindberg (23), Schneider et al. (28), and Walker et al. (34) considered the cerebral changes as a dynamic expression of a dying brain. They attributed this kaleidoscopic picture to a number of factors, Zander et al. (36).

By light microscopy, varied pathological changes are seen in the brains of comatose and apneic persons who have been on the respirator. These may be discussed for each anatomical unit.

Neuron.--The neurons of the cerebral cortex, basal ganglia and cerebellum are more frequently altered than those of the brain stem (table 4). However, the type of cell changes are similar although varying in degree in all parts of the encephalon. Many of the nerve cells have a clear case through which a few fine strands pass to the wall of the cell. The cell membrane, usually intact, may be scalloped. Nissl granules are not discernable in the dark staining cytoplasm that contains an eccentrically placed nucleus so diffusely stained that a nucleolus rarely can be identified. The nuclear membrane is often poorly defined and the pink granular nucleoplasm blends with the cell cytoplasm. In hemoatoxylin and eosin preparations, the perikarya of many neurons stains diffusely red (red neurons). In areas of necrosis, interstitial edema is pronounced.

In the diencephalon and brainstem, the necrosis and edema is less marked, but many neurons have homogenous pink cytoplasm within shrunken cell membranes (31).

In the cerebellum, the changes vary in the different layers of the folia. The small cells of the molecular layer are rarely severely altered; their nuclei and cell cytoplasm may stain darkly, but their general architecture remains.

At the junction of the molecular and Purkinje cell layers, edema fluid often separates the traversing fibers and surrounds the Purkinje cells. The latter show varied changes, sometimes appearing normal, in other brains completely lysed leaving an empty space in the tissue, and in other brains, swollen with pink-staining cyto- and nucleoplasm, often surrounded by a cuff of edema fluid. The granular cells tend to be the most severely changed, in many cases being necrotic and staining faintly, and in other brains being markedly attenuated with only a few dark staining nuclei remaining. The degree of involvement of the granular layer does not necessarily correspond to the state of the Purkinje cells, which may be preserved when the granular layer is lysed.

In the spinal cord and brain stem, the neuronal changes are similar to those in the diencephalon. The neurons are frequently shrunken with cytoplasm that stains homogeneously red. Frank necrosis is infrequent but neurons may be missing due to lysis (29).

Glia.--The glia of the cerebral cortex share in the severe changes. Both astrocytes and oligodendroglia in the cortical layers are swollen and their nuclei pyknotic. Swollen, hyanlinized astrocytes are rarely seen unless a lesion has been present for some time before death; nor is there a proliferation of fibrillary astrocytes. The oligodendroglia have swollen vacuolated cell bodies with pyknotic nuclei. If the cortex is markedly necrotic the oligodendroglia may be lysed and appear as a faint shell.

Microglia are lysed in the severely necrotic zones; only in areas of premortem infarction are there gitter cells which represent not changes related to the dead brain but premortem reaction.

Ependymal cells participate to varying degrees in the lytic process. In many cases the ependyma along the ventricle is well preserved and the cells show only a mild nuclear pyknosis. In other cases, the ependymal cells are swollen with eccentric and pyknotic nuclei. More commonly, however, in the subependymal layers, necrotic and edematous clefts are present (figure 6B). In these areas, there is no evidence of reactive change--no gitter cells, no astrocytic proliferation and no ependymal thickening of the ventricular wall.

The cells of the choroid plexus react somewhat similarly to the ependymal cells. In some cases there is little change except swelling of the cell body and pyknosis of the nucleus; in other cases, there are severe lytic changes with disintegration of the cell (figure 6A). The blood vessels of the choroid plexus show no significant changes although the interstitial tissue may have edema filled spaces.

White Matter.--That the white matter is involved in the lytic changes to a lesser degree than the cerebral cortex is generally accepted (7,19). True, myelinated nerve fibers entering the lower layers of the cerebral cortex are swollen but appear to have intact axons. In the underlying white matter, the U fibers and the myelinated tracts stain somewhat palely. Both astrocytes and oligodendroglia are identifiable; the latter rarely exhibit the swelling which is commonly seen in vascular or inflammatory insults of the brain. In severe cases, as Feigin et al. (7) have described both gray and white matter are edematous and necrotic. Usually the blood vessels of the white matter have little perivascular edema and no surrounding cellular reaction.

Meninges.--The pia arachnoid and dura mater appear relatively normal unless they are involved by the primary condition. In most cases, the subarachnoid space is free of inflammatory cells and blood; if blood is present, a premortem hemorrhage occurred. An exception to this statement is the necrotic and lacerated state of the cervico-medullary junction which may have a slight hemorrhagic infiltration as a result of the constant ballottement by the cerebellar tonsils which move with the fluctuating spinal fluid pressures transmitted from the respirator.

Cerebral blood vessels.--The cortical blood vessels have relatively thin walls and clear perivascular spaces. Thickened vessel walls are usually associated with premortem hypertensive conditions. The endothelial cells lining the small vessels of both the cerebrum and cerebellum do not appear edematous, irrespective of the state of the surrounding tissue. This is not in line with the early theories of Webster and Ames (35) who, to explain the no-flow phenomena, suggested that swelling of the capillary endothelium was responsible for the lack of blood flow in certain parts of the brain after temporary ischemia. However, Fischer and Ames (8) have recently admitted that this theory is not supported by further rheological studies which implicate changes in the blood viscosity. The pathological findings suggest that extravascular forces compress the walls of the smaller vessels and occlude the lumen.

The significance of the light microscopic findings is not entirely clear. It has been shown that the clear pericellular and perivascular spaces may occur in the postmortem period as the result of the passage of the tissue through dehydrating agents used in the embedding. Moreover, the darkly stained neurons may be produced by traumatic handling of the tissues. However, to consider all these changes as artifactual does not seem warranted for they are not uniformly present in the brain but are more prominent where the brain grossly appears swollen or edematous, and are more pronounced in areas of necrosis. A conservative interpretation of these findings would recognize that although most of the changes may be the result of postmortem handling of the tissues, they may also be an indication of premortem swelling and necrosis of the tissues.

RESPIRATOR BRAIN

The peculiar, almost unique, gross and histological alterations in the brains of persons artificially aerated has been termed a respirator brain (18). The implications of this term are not accepted by all neuropathologists for some consider the changes as not significantly different to the postmortem autolysis seen in brains removed long after death or improperly fixed. The concept of a respirator brain is more generally accepted in the United States of America than in European countries. According to the poll that Moseley et al. (26) made in 1976, 91 percent of the members of the American Association of Neuropathologists concurred in the designation of "respirator brain." However, there was less agreement as to what constituted that condition.

In descending order of frequency, the criteria considered to be required and their percentage acceptance were as follows:

1. No evidence of inflammation (97 percent)
2. Cortical congestion (91 percent)

3. Cerebral swelling (86 percent)
4. Cerebral softening (79 percent)
5. Cortical (cerebral) neuronal changes (75 percent)
6. Cerebral lysis and necrosis (69 percent).

Although some criteria met the approval of at least 70 percent of the neuropathologists responding to the questionnaire, when applied to the neuropathological findings in the collaborative study series as criteria for a respirator brain, only 28.6 percent of the patients diagnosed as having a respirator brain met all criteria. Obviously, the neuropathologists had weighed or omitted certain criteria in making their decisions (table 5). The omission of no one criterion, however, significantly improved the score. One must assume, and informal discussion confirmed the conclusion, that the examiners used a "gestalt" standard in making the decision of a respirator brain.

In keeping with the above criteria, the respirator brain might be described in the following terms:

The brain is dusky and swollen. The cerebellum is enlarged and is moulded about the brainstem and into the lateral recesses. Necrotic and often macerated tonsillar herniations are invaginated along the cervico-medullary junction. Apparently, from this macerated surface, fragments break away and are found lodged along the spinal cord or in the roots of the cauda equina. The consistency of the brain is usually soft and the brainstem so fragile that it is often torn in the process of removing the brain. Occasionally, (1 percent of cases) the brain is mushy. Even though it is placed in a fixative soon after death, it may not harden. In histological preparations, much of the brain has lost its usual staining characteristics. The neurons and glia have extra-, and to a lesser extent, intra-cellular edema with dissolution of cytoplasm, membranes and processes. In the diencephalon and basal ganglia, these changes may be less pronounced although there may be areas of necrosis. In general, the white matter is affected to a lesser degree. The pia arachnoid and cortical blood vessels are little involved except for perivascular edema. Frank thrombosis in arteries, veins or sinuses are rarely encountered. However, in spite of this severe necrosis, there is little or no inflammatory or cellular reaction of glia or hematogenous elements.

These alterations are essentially those that Kramer (21) described as intravital brain death and which he considered to be typical of "deanimation." He described three stages or degrees of pathological change but without sharp lines of differentiation. Schneider et al. (28) concluded that the early changes were autolysis and believed that pathognomonic findings of cerebral death are present only in the brains of individuals who have been on the respirator for at least 36 hours; by that time, alterations that they consider specific are apparent, namely migration of fragments from necrotic herniated cerebellar tissue into the spinal subarachnoid space, hemorrhagic softening of the upper cervical segments, and necrosis of the anterior lobe of the pituitary gland. However, not all of these changes can be demonstrated, even when sought for, if the period of artificial ventilation is brief.

These findings that Schneider et al.(28) consider specific merit some discussion. The migration of folial fragments about the spinal cord is found only in persons who have been on a respirator (12). Yet, in the first report of this condition the authors concluded that the subarachnoid implant was a heterotopia of embryonic origin (32). In a later report, the finding was considered a postmortem artifact (6). However, the nature and significance of this finding seems established as a necrotic fragmentation of the herniated cerebellar tonsils, probably as the result of ballottement of the herniating tonsils by the oscillations of the cerebrospinal fluid pressure caused by the respirator (14). The second specific finding, namely hemorrhagic softening of the upper cervical spinal cord, presumably results from the cerebellar herniation through the foramen magnum. Since this occurs in many conditions such as Arnold-Chiari malformation, tumor, etc., it probably should not be considered specific for a dead brain. The third change--the anterior pituitary necrosis--has been reported in cases of anterior transtentorial herniation and hence is not pathognomic of a dead brain. Accordingly, only the migrating cerebellar particles are specific for brain death.

The Nature of the Respirator Brain.--Some neuropathologists, however, maintain that the changes found in the respirator brain are due to postmortem autolysis and indistinguishable from the alterations resulting from delayed cooling or fixation of the brain (1). In this series, the delay between declaration of death and the postmortem examination was essentially the same in the case of brains diagnosed as respirator and nonrespirator (table 6). However, this may not be an appropriate method of determining postmortem delay because the respirator brains were probably nonmetabolizing on the respirator for longer periods than the nonrespirator brains.

Recognizing this circumstance, one would have to admit that there would be an element of postmortem autolysis in the brain of any patient declared cerebrally dead. Hence, the differentiation of ischemic changes occurring premortem (during circulation) and autolytic postmortem alterations (after arrest of circulation) are rendered more difficult because the biochemical processes involved are not very different. Both require enzyme reactions. In postmortem autolysis, the process is initiated by the unbalanced action of phosphatases and anaerobic glycolysis producing lactic and other acids. The resulting acidosis destroys mitochondria, lysosomes, or microsomes releasing their lytic and protein-splitting enzyme--cathepsin. Thus, long chain molecules of protein are broken down into smaller elements which increase the osmotic activity and water is drawn from the stagnant blood into cells and interstitial tissue (9). If these enzymes are destroyed by preheating the fresh tissue to 55°C or by cellular poisons, these changes do not occur and the brain tissue retains its normal appearance and staining reactions indefinitely.

Friede and van Houten (11) showed that certain postmortem changes in brain tissue resulted from anaerobic glycolysis. Incubation of rat cerebellar tissue in glucose in the presence of cyanide produced clasmatodendrosis of astrocytes and severe edema of the neuroglia in the Purkinje layer of the folia. Blocking glycolysis by sodium fluoride prevented these changes. If glucose-6-phosphatase was used, in addition to the above alterations, the granular cells became ballooned. These changes were indistinguishable from the so called postmortem lysis seen in human material. Further evidence came from Ikuta et al's (16) demonstration that lysis of the granular layer of the cerebellum was a postmortem phenomenon that required enzymes, the activity of which could be blocked.

In ischemic cell change, somewhat similar biochemical changes occur involving the enzymes of the citric acid cycle producing lactic acid; the resulting acidosis disrupts lysosomes releasing hydrolytic and other enzymes that break up the cell cytoplasm and draw water into the cell forming an eosinophilic substance (10,13). If sufficient circulation remains, the process may be repaired. The biochemical changes in autolysing and infarcting brains differ in degree but in addition, the autolysing brain has no circulation to furnish the necessary reagents to repair or react to the enzymatic disturbances. If, in total brain infarction the blood is recirculated by increasing the systolic blood pressure these reactive changes do occur (21). Thus, it is not unexpected that some features--swollen, discolored brain and red neurons--are particularly prominent in respirator brains, while others--softening and necrosis--are more common in postmortem autolysis. Confusion has arisen because of the assumption that all processes occurring after cessation of circulation (or circulatory "death") are autolytic, whereas reactions to ischemia are _in vivo_ processes. However, since some postmortem processes utilize the same enzyme system as the _in vivo_ ischemic changes, the alterations occurring after death may be predicated by the premortem state of the brain. Thus, if the enzyme systems are depleted in the agonal process, they are not available for postmortem autolysis. The essential difference between ischemic and autolytic changes lies in the fact that after cardiac death, the enzymes cannot be replenished by nuclear or cytoplasmic synthesis (20), because there is no circulation to carry essential metabolites for restitution of the cell constituents.

Lindenberg (23) suggested this hypothesis to explain the different cellular morphology he observed in brains removed at autopsy. On the basis of experimental studies, he concluded that ischemic changes occurring while cerebral circulation was intact could continue to operate after cardiac arrest, utilizing enzymes remaining in the tissue. Consequently, if as the result of a chronic illness, the brain became hypoxic prior to arrest of circulation and exhausted its supply of oxygen and the enzymes associated with Krebs cycle in the postmortem period, the encephalic structures could undergo little necrosis. Under such conditions the phosphocreatinine, ATP and ADP, were depleted and what glucogenic substance was present could not be utilized even anerobically so that little lactic acid was produced. On the other hand, if the brain had a large supply of enzymes and glucose, in the absence of oxygen after the cerebral circulation ceased, anerobic glycolysis would produce lactic acid and, according to Lindenberg, an acidosis at the rate of 0.15 of 1 pH/min, creating an optimal environment for the release of hydrolytic enzymes normally contained within lysosomes. This disturbance of the osmotic balance would cause a marked uptake of water by cells and interstitial tissue. Further evidence for this hypothesis has come from the work of Myers and Yamaguchi (27) who showed that food-deprived monkeys may recover from a 10-minute arrest of cerebral circulation, whereas glucose-infused animals develop seizures (myoclonic) and die within 2 days. The food-deprived animals have a moderate decrease in ATP to 0.08μ moles/g (control 2.08), moderately increases in lactate to 12.08μ moles/g (control 3.01), and an increased NaK-activated ATPase activity. In glucose-infused animals, 10 mins of circulatory arrest decreases ATP only to 0.14μ moles/g but it markedly increases cerebral lactate to 32.5μ moles/g. The brains of the fed monkeys are edematous, swollen and have an impaired blood-brain barrier resembling the respirator brain.

Thus, the line between premortem ischemia and postmortem autolysis is not as clear as it was conceived at one time. The situation is confounded by the cardiac-oriented concept of death, whereas insofar as the brain is concerned, death relates to the absence of cerebral, not systemic, blood flow. It seems that the changes in the granular layer of the cerebellum and the clasmatodendrosis of astrocytes occur after arrest of cerebral circulation, but the cellular changes (red neurons) may depend upon metabolic conditions before as well as after cessation of cerebral blood flow.

FACTORS INFLUENCING THE DEVELOPMENT OF A RESPIRATOR BRAIN

In view of the biochemical basis of a respirator brain, it seems possible that factors modifying the subject's internal environment might influence the development of the changes in the brain.

Time on the Respirator.--The time the subject remained on the respirator before death was declared seems to have an influence on the pathological changes in the brain (table 7). Of the patients artificially aerated up to 12 hours, only two of 15 had brains that were classified as respirator brains; of the 19 persons on the respirator 12 to 23.9 hours, five had brains that met the criteria for respirator brains; and of 67 patients artificially ventilated for 24 to 47.9 hours, 32 were considered to have respirator brains. Thereafter, for the next 96 hours, approximately half (36) of the 74 subjects had brains that were classified as respirator brains. After that time, the number dropped to approximately 33 percent. One interpretation of this sequence might be that some time is required for the criteria of a respirator brain to develop--approximately 24 hours.

Most investigators but not all (19) have noted this delay in the development of a respirator brain. The precise time required for the biochemical changes to occur is not agreed upon. Lindenberg (23) considers the period to be more than 6 hours; Matakas et al. (24) believe that 36 hours may be required. Probably factors related to the primary condition and to the type of pathophysiological disturbances may play roles in the dynamics of the state.

Primary condition.--The major conditions precipitating entry into this study and eventual death are listed (table 8). With the exception of trauma, the percentage of cases with respirator brains in the clinical categories is remarkably similar (40 percent). It would seem that the reactions to the common factor(s) producing brain death are more potent determinants of the neuropathologic changes than the primary diseases. In the one exception, the high incidence of intracranial hypertension in head injuries may account for the greater number of respirator brains.

The primary condition also plays a role in the time a patient will be on a respirator (table 9). Intracranial hemorrhage kills much earlier than infarctions but has about the same percentage of respirator brains.

Patients with hypothermia, arterial hypotension and absent cephalic reflexes, probably as the result of brainstem damage have a high percentage of respirator brains (34). However, medications prescribed for cerebral edema, infection or sedation have no apparent influence on the likelihood of occurrence of a respirator brain. Neither therapeutic hypothermia nor dialysis seemed to affect the degree of neuropathological change.

The basis of cerebral death in many European countries is the absence of cerebral blood flow and the pathological substrate is considered a totally infarcted brain. It would seem that this state represents the end point of a dynamic process which might take hours or even days to develop. Granted that a massive intracerebral hemorrhage may raise the intracranial pressure to the level of the systolic blood pressure within minutes, most conditions primarily responsible for cerebral death, require time for the molecular processes to produce cerebral edema. Although the release of hydrolytic enzymes initiates cerebral edema, much of the water must come from the cerebral blood vessels, and for the brain to increase in weight, some blood must be entering the cerebral circulation. Thus, before the cerebral circulation is completely blocked, the intracranial blood volume must be augmented at least temporarily. Most authors considered that the cessation of cerebral blood flow is the result of compression or occlusion of intracerebral capillary or venous channels. Towbin (33) however has advanced the hypothesis that the congestion and edema results from venous or sinus thrombosis. Kimura et al. (18) and Lindenberg (23) have also noted the occurrence of sinus thrombosis in such brains. In the collaborative study a careful search was made for such thrombi. In only 14 percent of cases were thrombi found in the sinuses; some of these clots were probably agonal, a not uncommon finding in patients with intracranial hypertension. But the fact that in more than half of the cases the sinus walls were smooth and glistening would suggest that sinus thrombosis is not the usual cause of the intracranial hypertension.

Minimal Period of Cerebral Anoxia for Cerebral Death.--Granted that tha anatomical substrate of cerebral death takes hours or days to evolve and does so both in circulation (premörtal) and post circulation (postmortal) states, the question may be asked as to when this process reaches an irreversible stage.

Clinicians do not agree on the time that a brain may be anoxic and yet recover. Periods from a few minutes to more than an hour have been suggested depending upon the environmental conditions, temperature of the brain, the presence of cerebral depressants, the type and degree of anoxic insult and probably the pre-anoxic state of the brain. Certainly under hypothermic conditions, the human cerebrum may tolerate interruption of its circulation for more than an hour (15).

Even under normothermic conditions in experimental animals, the cerebral circulation may be absent as long as an hour with return of electrical activity and preservation of parts of the brain if postischemic brain edema is prevented. Sobotka et al. (30) interrupted the perfusion of an isolated, normothermic dog's head for 60 minutes. Areas of intact brain correlated with electrophysiological, biochemical and metabolic restoration of brain function. Leninger-Follert and Hossmann (22) studied the cortical blood microflow and oxygen tension after an hour's cerebral ischemia in normothermic cats. When cerebral swelling was prevented, the cortical microcirculation and oxygenation returned to normal levels.

Barbiturates have been shown to depress the cerebral metabolism so that long periods of anoxia may not produce irreparable damage (25). Intracerebral and extracerebral insults causing anoxia produce different pathological states (34), and finally if some cerebral circulation even of a nonoxygenating solution is maintained to wash out acidic products, long anoxic episodes may be tolerated (15).

Perhaps a more practical question relates to the minimal time at which anoxia under normal circumstances can produce irreversible brain changes. Several investigators have addressed this question. Webster and Ames (35) found that rabbit retinas deprived of oxygen and glucose for up to 20 minutes had swelling of mitochondria, loss of synaptic vesicles and swelling of the Golgi membranes and granular endoplasmic reticulum which were considered reversible. By 30 minutes, multiple discontinuities had appeared in the cell and organelle membranes which allowed free passage of solutes and irreversibly altered the chemical composition of the fluids within the organelles and cytoplasm. Thus, the restorative capabilities of the cell were lost. Garcia et al. (13) believe that in global ischemia the histopathological cellular changes noted after 17 minutes of anoxia are consistent with cell death.

CORRELATION OF CLINICAL AND PATHOLOGICAL CRITERIA OF CEREBRAL DEATH

It is logical to expect that there should be a high correlation of a respirator brain with those clinical examinations suggesting a functionless brain. Aside from the neurological examination, electroencephalography (EEG) is the most commonly used method to test brain function.

EEG and Neuropathological Findings.--*A priori*, one would assume that a dead brain would be associated with an isoelectric record of the brain waves. However, a perfect correlation could not be expected because the EEGs were often made hours or even days before the patient was declared dead by reason of a nonfunctioning brain or heart. On the other hand, the clinical and EEG manifestations of a dead brain in 43.2 percent of cases were present less than 24 hours before cardiac arrest--too short a time for the changes of a respirator brain to develop. As seen in table 10, cases with biological activity (BA) in the last EEG recorded are associated with fewer swollen brains, less cerebral herniations and fewer respirator brains than cases without evidence of electrical activity (electrocerebral silence, ECS). The patients with equivocal EEG's seem to comprise a group with pathological changes between the other two classes.

The presence or absence of brain waves also relates strongly with the likelihood of a respirator brain (table 11). Although ECS is present in many cases that do not have a respirator brain, an active EEG correlates highly with a nonrespirator brain. Of 12 patients with biological activity in the EEG and a respirator brain, three had not had a record taken for one or more days, and in at least 5 cases, the diagnosis of a respirator brain might be questioned. The large number of cases with ECS but a nonrespirator brain is probably due to the patients dying within the first 24 hours (28 percent) before changes of a respirator brain can occur. Yet, the brain may be irreparably and lethally damaged without having all the clinical and EEG criteria of cerebral death, or a respirator brain at autopsy.

The Pathophysiology of a Dead Brain.--In clinical practice, the usual cause of a dead brain is the absence of cerebral blood flow which may result from either intracranial hypertension exceeding systolic blood pressure or cessation of systemic blood flow commonly due to cardiac arrest. If the EEG and neuropathological findings are analysed in two such groups of cases (table 12), it is apparent that not only the EEG findings differ in the two groups ($p=<.001$) but the neuropathological findings are dissimilar. In cases of increased intracranial pressure from brain injuries, electrocerebral silence, cerebral herniations and intracranial hemorrhage are much more common than in cases of impaired perfusion pressure in which biological activity in the EEG, cerebral infarctions and nonrespirator brains are more often encountered.

If the clinical criteria of cerebral death are met, one would expect that the neuropathological findings should confirm this conclusion. The clinical criteria of cerebral death are generally agreed upon but the neuropathological findings in such cases are less well defined. However, if it is assumed that the minimal neuropathological criteria of a dead brain are those of a respirator brain, the correlation of clinical and brain pathology may be examined in the collaborative study. A few postulates should be accepted.

(1) That the clinical criteria of a dead brain are coma, apnea, absent cephalic reflexes and an isoelectric electroencephalogram.

(2) That a neuropathological diagnosis of a respirator brain is adequate to establish a dead brain.

(3) That the patient was on the respirator for 24 hours after the clinical diagnosis of cerebral death was established. This period is necessary to allow the pathological changes consistent with a respirator brain to develop.

Assuming these basic postulates, one may examine the material of the collaborative study (table 13). It is apparent that the clinical diagnosis of cerebral death is associated with a respirator brain in 85.2 percent of cases as compared to 15.5 percent respirator brains among the remainder of the autopsied cases ($p<0.001$). However, if the 12 cases having a clinical diagnosis of cerebral death but nonrespirator brains are analysed individually, it becomes apparent that certain attenuating factors are present. Seven patients had severe brainstem damage which might have induced spurious areflexia and ECS on the basis of a low blood pressure. There remain 5 cases in which there is no obvious explanation for the absence of the findings of a respirator brain; perhaps these brains had exhausted their supply of lytic enzymes in the late stages of the primary illness before clinical manifestations of cerebral death became apparent.

SUMMARY

The pathological findings in the brains of a series of 240 patients who, because of coma and apnea, required artificial respiration are presented.

The gross alterations, aside from those related to the primary intracerebral lesion, run the gamut from minor changes such as may be found in the brain of any person dying of a systemic disease to the soft, soggy and gelatinous state characteristic of postmortem autolysis.

Although the minimal time for irreversible changes to occur under normal environmental, internal and external, conditions is 17 minutes, the enzyme and other processes that cause chemical and structural changes recognizable by light microscopy, may require from 12 to 36 hours to develop. Hence, gross and microscopic confirmation of brain death might not be apparent for approximately 24 hours.

The pathological changes characterizing a respirator brain were present in 85 percent of the cases meeting the clinical criteria of cerebral death for 24 hours. In some of the other cases diagnosed as cerebrally dead, irreparable brainstem damage could account for the clinical findings.

The differentiation between the findings of a respirator brain and those of postmortem autolysis is to some extent, confused by the similarity of agonal and postmortem processes.

The presence of a respirator brain correlates with the absence of electroencephalographic activity.

TABLE 1

Centers and Neuropathologists

Clinical Centers	Project Neuropathologists
Massachusetts General Hospital Boston, Massachusetts	E. Pierson Richardson, M.D.
New York University New York, New York	Irwin Feigin, M.D.
Northwestern University Chicago, Illinois	Jan E. Leestma, M.D.
Ohio State University Columbus, Ohio	Leopold Liss, M.D.
University of California San Diego, California	Peter Lambert, M.D.
University of Pennsylvania Philadelphia, Pennsylvania	Lucy Rorke, M.D.
University of Utah Salt Lake City, Utah	Margaret Grunnet, M.D.
Virginia Commonwealth University Richmond, Virginia	William Rosenblum, M.D.
College of Physicians and Surgeons New York, New York	David Cowen, M.D.

Neuropathology Review Panel

Stanley Aronson, M.D.
Providence, Rhode Island

Jann Brown, M.D.
Los Angeles, California

David Clark, M.D.
Lexington, Kentucky

Kenneth Earle, M.D.
Washington, D.C.

Bruce Konigsmark, M.D.*
Philadelphia, Pennsylvania

William McCormick, M.D.
Iowa City, Iowa

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*Deceased

TABLE 2

Time on Respirator*

Elapsed Time	No. of Cases	Resuscitation Stopped (Cases)
(hour)		
0 - 1	4	0
1 - 5.9	51	6
6 -11.9	33	5
12 -23.9	63	16
(days)		
1 - 1.9	143	68
2 - 2.9	54	11
3 - 3.9	33	4
4 - 6.9	35	2
(weeks)		
1 - 1.9	21	1
2 - 3.9	13	1
4 +	9	0
Totals	459	114

*Based on time of entering study to death; some patients may have been on artificial respiration before admission to hospital and study.

TABLE 3

Organs Examined at Autopsy

Organ	Number of Cases
Brain only	21
Brain and spinal cord	8
Brain and dura mater	21
Brain, spinal cord and dura mater	25
Brain and general autopsy	17
Brain, spinal cord and general autopsy	23
Brain, dura mater and general autopsy	34
Brain, spinal cord, dura mater and general autopsy	71
General autopsy alone (no brain or spinal cord)	10
Unsatisfactory central nervous system specimens (but partial examinations in six cases)	10
Total	240

TABLE 4

Relationship of Type and Location of Lesion

	Location of Lesion					
	Total Number of Cases					
Type of Lesion	Cortex	Diencephalon	Cerebellum	Brainstem	Medulla	Spinal Cord
None	11	38	36	35	97	76
Infarction	38	28	23	27	7	3
Hemorrhage	32	28	18	36	4	5
Edema	63	46	37	42	27	16
Necrosis or lysis	26	24	42	23	13	6
Neuronal loss	29	29	32	23	8	8
Other	12	19	23	25	58	102

TABLE 5

Brains Reported as Having No Pathological Changes at Some Sites but Coded as Respirator Brain

Site	No. of Brains No pathology	 Respirator brain
Spinal cord	83	31
Cervical-medullary junction	105	34
Brainstem	38	6
Cerebellum	39	3
Diencephalon	40	6
Cortex	14	1

TABLE 6

Relationship of Time to Autopsy to Neuropathological Findings

Elapsed time (hours)	Number of cases	Respirator Brain			
		No		Yes	
		Number	Percent	Number	Percent
0 - 5.9	49	29	21	20	22
6 - 11.9	32	21	16	11	12
12 - 17.9	50	30	23	20	22
18 - 23.9	47	26	19	21	23
24 -	48	29	21	19	21
Total	226	135	100	91	100

TABLE 7

Relationship of Time on Respirator to Respirator Brain

Elapsed time on Respirator (hours)	No. of Cases	Respirator Brain No	Respirator Brain Yes
<12	15	13	2 (13%)
12 - 23.9	19	14	5 (26%)
24 - 47.9	67*	35	32 (48%)
48 - 71.9	33	16	17 (51%)
72 - 95.9	25	15	10 (40%)
96 -119.9	16	7	9 (56%)
120 -143.9	12	7	5 (42%)
144 -167.9	6	4	2 (33%)
>168	33	24	9 (27%)

*The peak at this time interval represents the cases on which resuscitation was stopped at 24 hours.

TABLE 8

Relationship of Primary Diagnosis to Respirator Brain

		Type of Brain	
	Total	Non-Respirator	Respirator
		No. of Cases (percentage)	
Primary diagnosis	226	135 (60)	91 (40)
Cardiac	42	27 (64)	15 (36)
Trauma	52	25 (48)	27 (52)
Cerebrovascular	69	40 (56)	29 (44)
Thrombosis	[13]	[6] (46)	[7] (54)
Embolism	[4]	[4]	--
Hemorrhage			
parenchymal	[26]	[14] (53)	[12] (47)
subarachnoid	[20]	[11] (55)	[9] (45)
Other	[6]	[5]	[1]
Infection	11	7 (64)	4 (36)
Exogenous Intoxication	4	4	--
Metabolic	21	15 (71)	6 (29)
Neoplasm	5	3	2
Other	22	14 (64)	8 (36)

TABLE 9

Relationship of Neuropathological Diagnosis to Time on Respirator

Neuropathological Diagnosis	Total	Time on Respirator (hours) 0 --	12 --	24 --	48 --	72 --	998 --
		Number of Cases					
	240	16	19	71	33	99	2
Normal	10	--	--	2	1	7	--
Infarction	44	3	2	7	3	29	--
Hemorrhage	82	5	8	34	14	21	--
Trauma	24	3	3	4	2	11	1
Tumor	4	--	--	1	1	2	--
Edema	34	2	1	8	9	14	--
Infection	5	1	--	2	--	2	--
Other	17	1	4	5	2	4	1
Unknown	6	--	1	4	1	--	--
Not examined	14	1	--	4	--	9	--

TABLE 10

Relationship of Appearance of Brain to Last EEG

EEG Diagnosis	Number	Appearance of Brain (%)							
		Swelling			Herniations			Respirator Brain	
		None	Generalized	Other	None	Transtentorial	Other	No	Yes
Equivocal	14	2(14)	8(57)	4(29)	3(21)	10(71)	1(7)	10(71)	4(29)
BA	67	36(54)	13(19)	18(27)	42(63)	15(22)	10(15)	58(87)	9(13)
ECS	144	16(11)	91(63)	37(26)	21(15)	93(65)	30(21)	66(46)	78(54)

TABLE 11

Relationship of EEG Activity to Respirator Brain

EEG Diagnosis	Respirator Brain Yes	 No
Equivocal	1	4
Always BA	12	60*
Always ECS	51	53*
BA, then ECS	26	17
Mixed, ECS or BA then ECS	1	1
Total	91	135

*p= <.001

TABLE 12

Comparison of EEG and neuropathological findings in cases of extra - (cardiac) and intra - (trauma) cranial disorders

EEG (final exam)	Cardiac Disease Number of Cases	Cerebral Trauma Number of Cases
BA	62 (5)*	15 (7)*
ECS	36	72
Neuropathological Diagnosis		
Normal	2	--
Infarction	14	3
Hemorrhage	5	29
Trauma	3	19
Tumor	1	--
Edema	9	--
Other or unknown	13	3
Herniations	27/47	48/54
Respirator Brain	15/42	27/52

*Equivocal records

TABLE 13

Correlation of Clinical, EEG, and Pathological Findings in Subjects on the Respirator at least 24 hours (146 cases).

State of CR & EEG (Final Examination)	Respirator Brain No. of Cases	Non-Respirator Brain No. of Cases
Absent cephalic reflexes and ECS	69	12*
Absent cephalic reflexes and not ECS	3 †	20
Present cephalic reflexes and ECS	1 ‡	3
Present cephalic reflexes and not ECS	5 §	33
Total	78	68

*These cases had the following qualifying factors: (a) brainstem damage was the primary lesion in 7 cases, (b) cortical lesions were present in 4 cases, (c) the histopathology was unknown in 1 case.

†Two of these patients had so much EKG and muscle artifact in their records that neither BA or ECS could be diagnosed; the record on the other patient was made 5 hours before death.

‡The last clinical examination on this patient was made 30 hours before death.

§EEG's and clinical examinations were made 1, 9, 60, and 208 hours before death in 4 cases; the fifth case had brainstem damage.

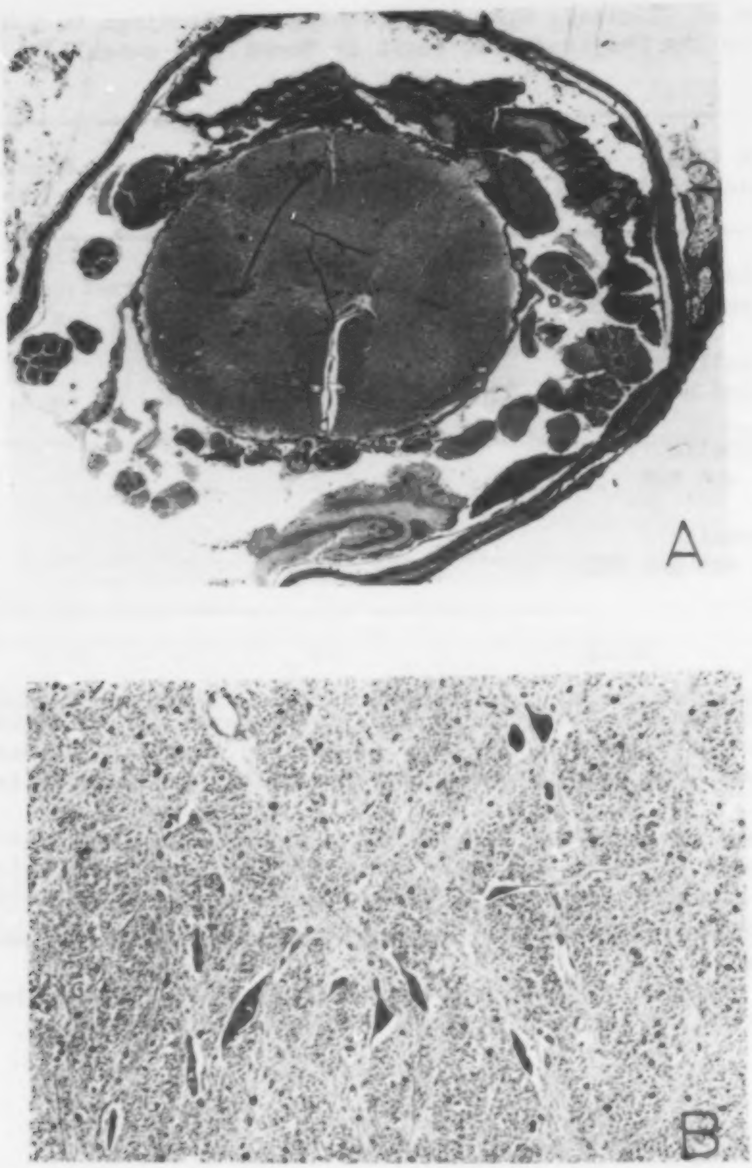

Figure 1. (A) Female, 45 years old, intracerebral hemorrhage, on respirator 5 days, respirator brain. Section of lumbar cord to show cerebellar fragments packed about the cord and nerve roots, hematoxylin and eosin stain (H & E, X 6). (B) Male, 55 years old, drug coma, on respirator 2 hours, questionable respirator brain. Homogeneous dark staining anterior horn cells of the cervical spinal cord in an intact normal matrix of fibers.(H & E, X 150)

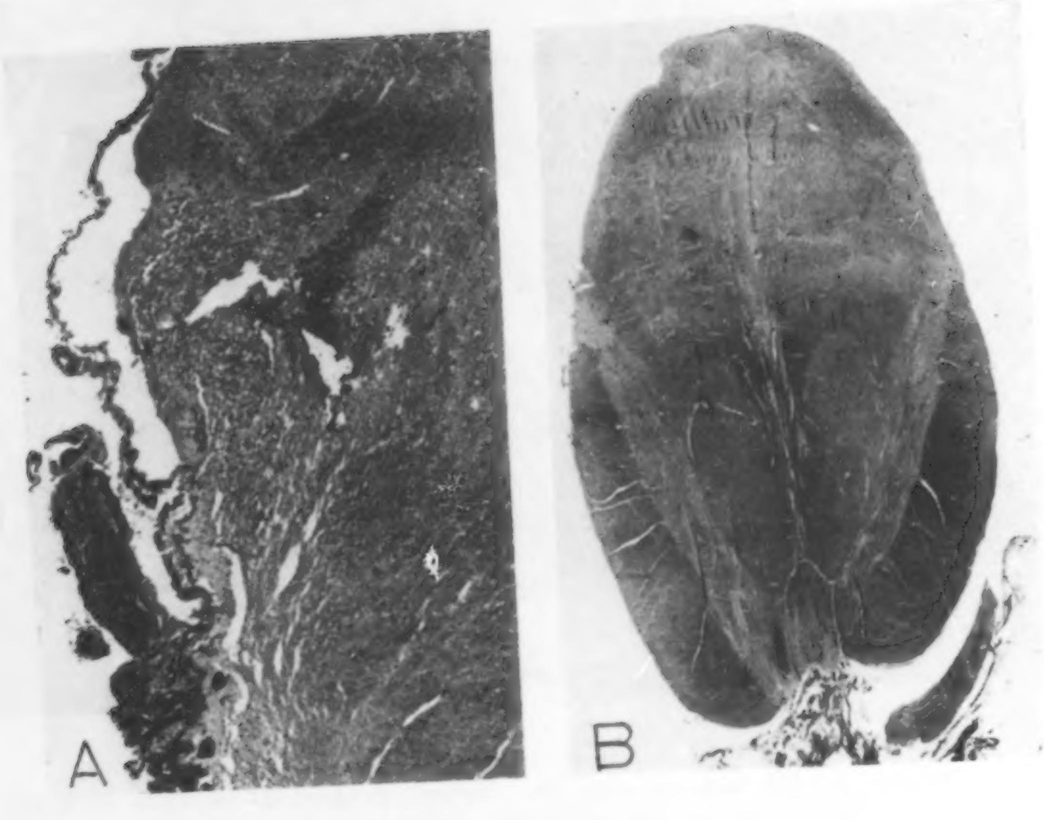

Figure 2. (A) Female, 62 years old, cerebral thrombosis on respirator 3 days, respirator brain. Laceration of cervical medullary junction presumably due to mechanical trauma of herniating tonsils(H & E, X 25). (B) Male, 19 years old, cerebral trauma, on respirator 1 day, non-respirator brain. Mesencephalon compressed and distorted by transtentorial herniations with a few flame-shaped hemorrhages at the basis pedunculi.(myelin stain, X 4)

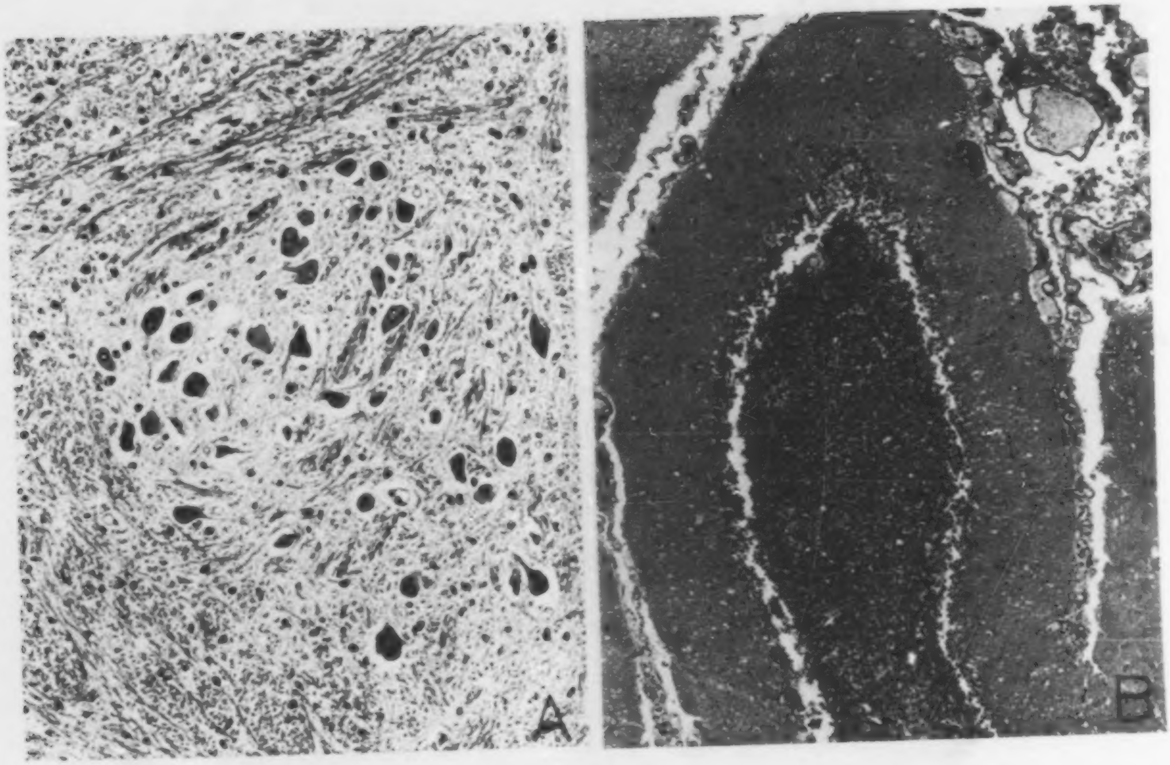

Figure 3. (A) Same as case 1B. Spinal trigeminal nucleus showing homogenous dark staining and shrunken cells with few nuclei discernable (H & E, X 175). (B) Female, aged 11, postoperative aqueductal stenosis, on respirator 11 days, respirator brain. Necrosis and edema of the Purkinje cell layer and lytic changes of the granular cells.(H & E, X 70)

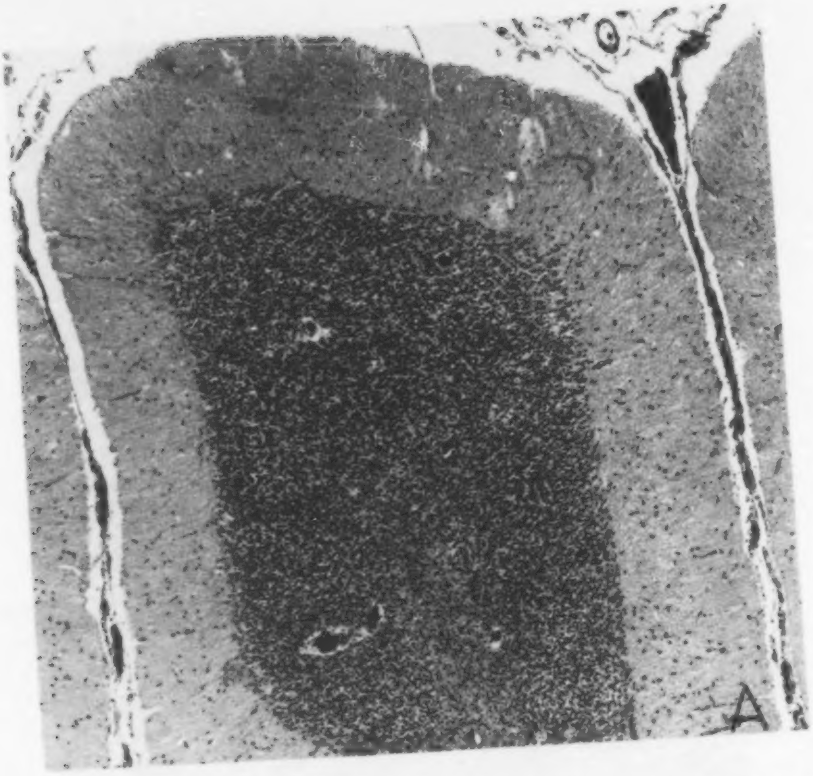

Figure 4. (A) Female, 4 years of age, postoperative fourth ventricle ependymona, on respirator 12 days, respirator brain. Marked loss of the granular cells and almost complete loss of Purkinje cells.(H & E, X 50)

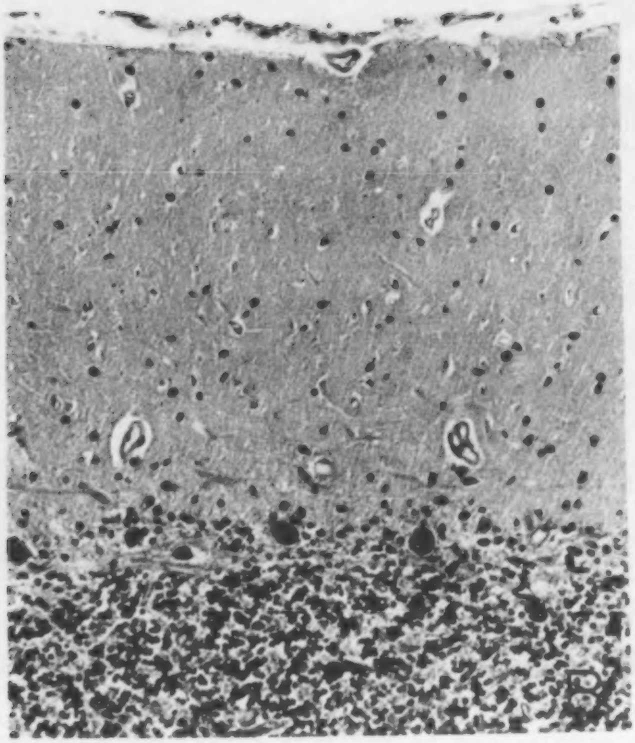

Figure 4. (B) Same as 1B. Mild changes in the arachnoid and in the molecular layer of the cerebellar folia; diffusely pyknotic Purkinje cells and lysed granular layer. Note the compressed vessels containing few erythrocytes. (H & E, X 175)

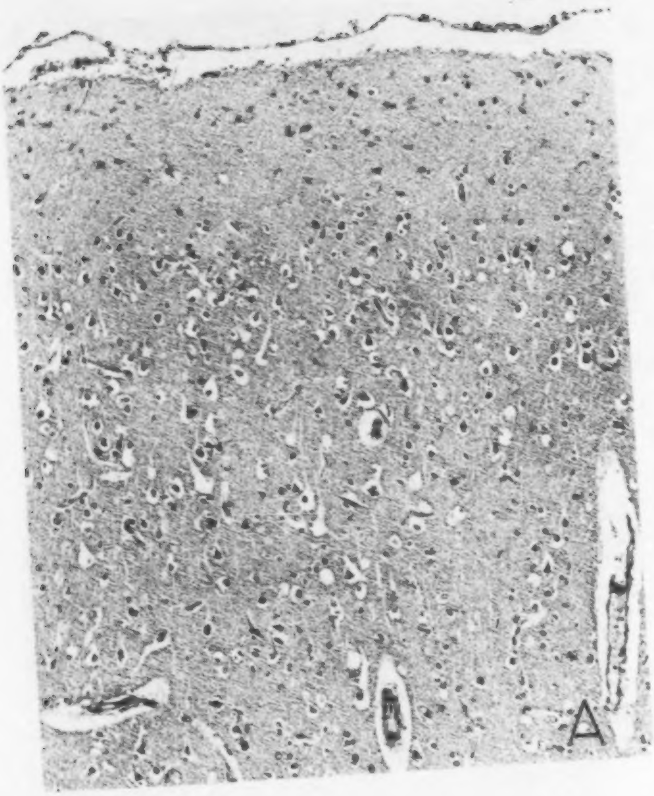

Figure 5. (A) Male, 42-year-old, cardiac infarction, on respirator 12 days, respirator brain. Section from the prefrontal cerebral cortex to show pyknosis of cell cytoplasm, lysis of cells and edema. Note that the arachnoid and the outer two cortical layers which have a mild astrocytic proliferation are relatively intact. The small blood vessels of the cerebral cortex are compressed. (H & E, X 100)

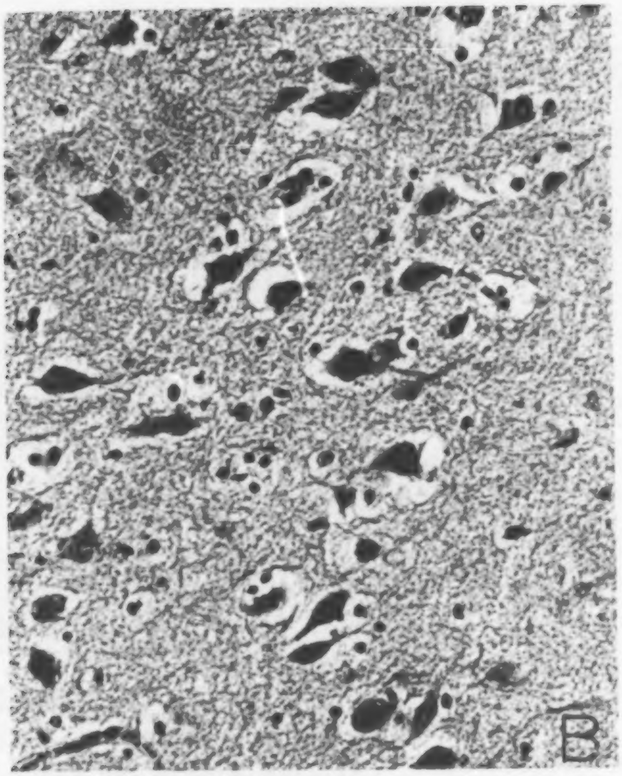

Figure 5. (B) Female, 64 years old, cerebral thrombosis, on the respirator 16 days, respirator brain. Section from the medial temporal cortex to show swollen homogenous, pink staining cytoplasm and indistinct pyknotic nuclei of neurons. Note the swollen satellite cells. (H & E, X 175)

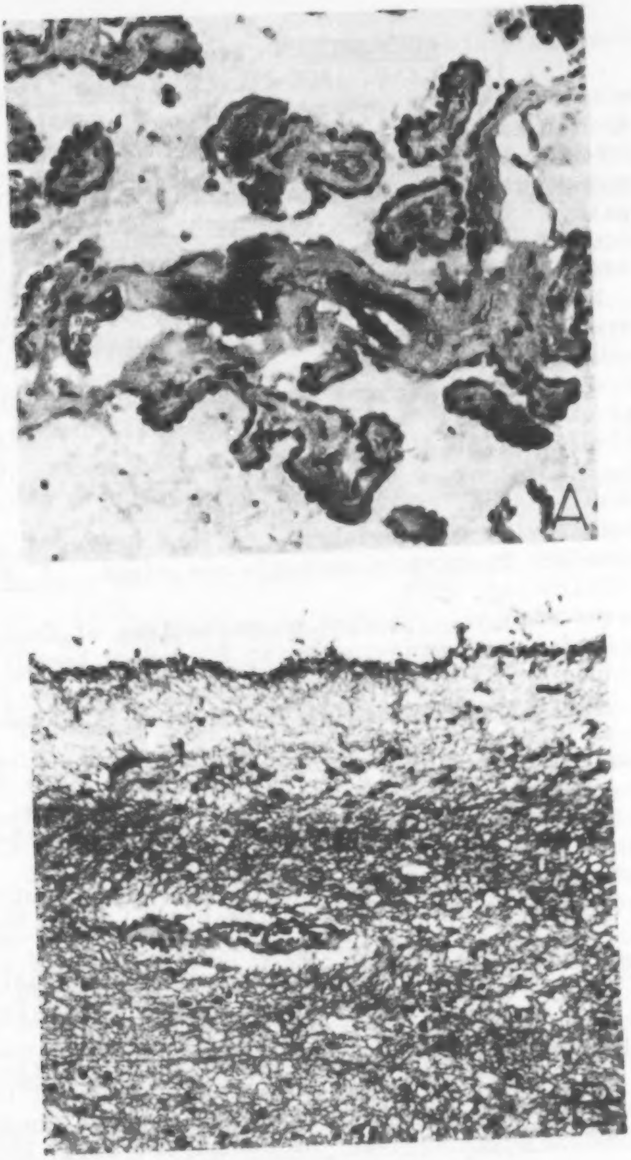

Figure 6. (A) Male 54-year-old with intracranial pressure, on respirator 21 days, respirator brain. Choroid plexus of the fourth ventricle has necrosis and edema of papilla and pyknotic nuclei of plexus cells. Note the congested vessels in the papillae. (H & E, X 200) (B) Same case as 6A. Ependyma of the fourth ventricle to show pyknosis and lysis of ependymal cells and subependymal necrosis. (H & E, X 150)

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CLINICAL CRITERIA OF BRAIN DEATH

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INTRODUCTION

Since the original recognition of the phenomenon of cerebral death in subjects whose vegetative functions were maintained in resuscitation units, a continuing assessment has been made of the necessary clinical criteria which must be met to predict the existence of this condition. Mollaret and Goulon and Mollaret et al. in 1959 described four grades of coma and proposed that the fourth or most severe grade be termed coma dépassé (a state beyond coma) in which there was not only total loss of sensory, motor, and conscious functions of the brain but also of vegetative functions (1, 2). Their description of this protracted state of brain death or "respirator brain," based upon 23 cases, included not only the description of the isoelectric EEG but also explicit clinical conditions. The latter included profound coma and absence of any clinical response to stimuli. With respect to the cephalic reflexes, the pupils were dilated and there was loss of pupillary light reflex, menace response, and corneal reflexes. No eye movement was elicited on head rotation, there was no swallowing, and the jaw sagged. There was loss of tendon reflexes, hypotonia, loss of medullary automatisms, and sphincter incontinence. Plantar responses were indifferent and idiomuscular contractions were preserved. In addition, there was absence of respiratory movement after stopping artificial respiration, cardiovascular collapse immediately after stopping intravenous norepinephrine, and hypothermia or hyperthermia in the absence of physical methods for control. Mollaret and Goulon also referred to a state called coma carus (deep coma) in which there was loss of conscious, sensory and motility functions but with incomplete disturbances of vegetative functions (1).

During the next decade, there developed widespread recognition by physicians of the concept of brain death but uncertainty as to the criteria for its recognition. In 1968, the ad hoc committee of the Harvard Medical School examined the definition of brain death and published its conclusions, which were widely accepted (3). The first part of the definition was expressed in terms of clinical criteria. These included coma with a state of unreceptivity and unresponsivity. Complete absence of spontaneous respiration was required and could be established by the absence of any effort to breathe during a three-minute period off the respirator. Lack of spontaneous movements or of any movements to stimuli over a period of at least 1 hour of observation was also specified. Pupils were required to be fixed and dilated and not responsive to light. Other cephalic reflexes which should be absent included: ocular movement to head turning, ocular movement to caloric irrigation, blinking responses, corneal reflex, pharyngeal reflex, swallowing, yawning and vocalization. It was stated that "as a rule the tendon stretch reflexes cannot be elicited" and that there should be no evidence of postural activity including decerebrate responses. The flat EEG was considered of great confirmatory value. It was necessary that hypothermia and intoxication by central nervous system depressants be excluded. The continuance of these conditions for 24 hours was required.

Subsequently, the reports of Silverman and associates emphasized the importance of an isoelectric EEG, recorded under strict technical conditions, in the identification of cerebral death (4). A number of reservations were expressed, however, for exclusive reliance upon the EEG in the determination of cerebral death. These were summarized and affirmed by a report of the Task Force on Death and Dying of the Institute of Society, Ethics and the Life Sciences in which the need for clinical determinations as principal criteria were affirmed as well as the impossibility of declaring a state of brain death in an individual still breathing and with cerebral reflexes present (5).

On the other hand, evidence has been presented that the Harvard criteria are excessively strict. It has been observed that spinal reflexes need not be lost in brain death (6, 7). The necessity of dilatation of the pupil has been questioned (7, 8). It has been argued that the persistence of complex movements, processed at a spinal level, can often occur in the condition of complete brain destruction (9). Recently, a requirement of vascular collapse has been affirmed by one group (10); whereas, it has been recognized as not essential by others, including the criteria adopted by the Memorial Hospital for Cancer and Allied Diseases in New York (7).

The presentation will deal with the clinical data accumulated in the prospective Collaborative Study of Cerebral Death and will relate clinical patterns and their time courses to ultimate outcomes, such as various states of survival or brain death as judged by the Harvard or modified criteria or by pathological examination. The problem of prediction of irreversible injury prior to collapse of autonomic function will be examined. The discriminative value of various clinical tests will be rated against known outcomes. Specific attention will be directed to the necessity of spinal reflex activity in diagnosis of brain death as well as to the status of brain stem reflexes. Pitfalls in diagnostic tests will be sought and recommendations made for clinical criteria.

METHODS

Data analyses were performed on two groups of patients. The first was based on 503 patients having coma and apnea as a condition of admission to the Collaborative Study of Brain Survival. The second utilized a subset of 102 patients observed in Center 6 (Ohio State University Hospitals). Clinical examinations were scheduled to coincide as closely as possible with electroencephalographic recordings. Upon notification of the existence of coma and apnea in a candidate for this study, the neurological examination was planned as a first step, followed as closely as possible by the EEG. In subsequent examinations clinical observations could either be done prior to the EEG or after it. Examinations were performed by the center director or his designees, who were trained in the system of examination.

Under the protocol followed, a state of cerebral unresponsiveness was considered to exist when the patient exhibited no apparent awareness of externally applied stimuli, obeyed no command, and did not phonate either spontaneously or secondary to a painful stimulus. Spinal or brain stem nociceptive or postural reflexes were distinguished from cerebral responses on the basis of recognized pattern, stereotyped nature of response, and stimulus specificity. Patients with the conditions of akinetic mutism and "locked-in syndrome" were excluded from the study unless they progressed to the state of complete cerebral unresponsiveness.

In the definition of apnea, original consideration was given to the Harvard criterion which specified absence of spontaneous respiratory movements when off the respirator for three minutes, provided that the arterial carbon dioxide tension was within normal range and that the patient had been breathing room air for at least 10 minutes before the trial (3). The safety of this procedure was questioned, and it was considered potentially hazardous to an already damaged brain to undergo such a test for three or more minutes. Consequently, lack of spontaneous respirations was inferred from the patient's need for continuous controlled respirations as determined by the attending physician and by the lack of any observed effort of the patient to override the respirator or by a ventilatory effort or movement other than that induced by the respirator. It was left to the center examiners to recognize the occasional patient with chronic pulmonary disease and long standing hypercapnia who might temporarily have respiratory cessation during artificial ventilation.

Vital signs were recorded at the time of the examination or from the clinical chart if observed within 30 minutes of examination. Blood pressure was measured by brachial cuff manometer. Pulse rate was noted or, if undetectable, cardiac rate. Body temperature was generally measured by rectal thermometer. Respiratory rate indicated either the spontaneous rate or the rate of the respirator.

Ten cephalic reflexes were observed in all cases except when examination was impossible because of local injury, absence of a body part, surgical dressing or intubation. In addition, the size of each pupil was measured in millimeters and recorded. The reflexes and their methods of elicitation were as follows:

Pupillary reflex - any direct or consensual response of the pupil to a bright flashlight.

Corneal reflex - a unilateral or bilateral contraction of the orbicularis oculi by touching each cornea with a wisp of cotton.

Oculocephalic reflex (doll's eye response) - contraversive conjugate eye deviation produced by brisk passive movement of the head from side to side and up and down. If absent, the eyes remain centered in the primary position.

Vestibular reflex (caloric response, oculo-vestibular reflex) - the ocular movements induced by caloric stimulation of the lateral semi-circular canal. After the external auditory canal was examined to ascertain the tympanic membrane was intact and impacted cerumen was absent or removed, the head was elevated to 30° above the horizontal (unless contraindicated by requirements or patient management). A small catheter was inserted into the external auditory canal near the tympanic membrane and 10 cc of ice water (0° C) were slowly introduced from a syringe. The reflex was considered present if nystagmus or ocular deviation occurred.

Audio-ocular reflex (audito-orbicularis reflex, cochleopalpebral reflex, auditory-palpebral reflex, auditory blink reflex) - contraction of the orbicularis oculi muscle in response to a sudden loud noise such as a sudden sharp hand clap near the ear.

Snout reflex (perioral facial reflex, orbicularis oris reflex) - the pursing, puckering or protrusion of the lips in response to the tap from a reflex hammer delivered to a tongue blade placed over the closed lips or directly to the upper lip in the midline.

Cough reflex - coughing response to irritating the trachea or bronchi which may occur spontaneously due to mucus or as a result of a suction tube being placed into the trachea via an endotracheal tube.

Pharyngeal reflex (gag reflex) - contraction of constrictor muscle of the pharynx or elevation of the palate upon touching the posterior pharynx with a tongue blade.

Swallowing reflex - deglutition when an object or drop of liquid is placed on the retropharyngeal mucosa.

Jaw jerk (masseter reflex) - the muscle contraction of the masseter muscles tending to close the jaw when the point of the jaw is tapped with the reflex hammer.

The first five reflexes were examined on each side while the last five were considered bilateral responses. The stretch, or tendon, reflexes were elicited on each side as the biceps, triceps, radial, knee and ankle jerks. Muscle tone was estimated on each side at elbow flexors and extensors and knee flexors and extensors. The abdominal reflexes and the plantar responses were examined on each side. Spontaneous or voluntary movements were noted and recorded in respect to jerks, spasms, shivering or other responses. Responses to nociceptive stimuli were tested on both sides at arm, leg and face. The embrace (Moro response) was considered as present when pinprick stimulation of the skin, of the upper arm, or lateral chest wall resulted in a typical embrace response of the arms. If present, it was described and recorded. Abnormal postures were specifically examined and recorded with respect to decorticate and decerebrate spasms or other patterns.

Ophthalmoscopic examination was performed and, in a latter phase of the study, specific notation was made for normal retina, pallor, papilledema, sludged blood, or other abnormality.

In order to gain some data on the incidence of cephalic reflexes considered not to be present in 100 percent of the normal population, a survey of 76 normal subjects and 41 hospitalized patients was carried out at Center 6.

In analyzing the value of clinical signs, it was necessary to observe correlations with precisely defined conditions, such as electrocerebral silence with coma and apnea for a specified time period or a pathological diagnosis of brain death (respirator brain). This was not possible with the 503 cases of the major study. In order to accomplish such analyses, the subset of 102 cases from the Ohio State University Center and 44 survivors from the entire group were utilized. In these subsets, phi coefficient was used to evaluate the ability of individual clinical tests to discriminate cases of presumptive cerebral death from other outcomes. The chi square technique was used to test the significance of the phi coefficients. For purposes of comparing clinical patterns in various groups, the 102 patients of Center 6 were divided according to the following outcomes: (1) presence of coma, apnea, and ECS (electrocerebral silence) for 24 hours or more regardless of whether somatic death occurred by cessation of resuscitative efforts or by cardiac arrest, (2) the presence of these same criteria for 12 hours, (3) presence of these criteria for less than 12 hours, (4) death from cardiac arrest without ECS ever having occurred, and (5) survival. In addition, after review of Center 6 neuropathological findings, a group of cases was identified as brain death on the strict definition of coma, apnea, ECS, and absence of cephalic reflexes (other than jaw and snout) for 24 hours and with a diagnosis of respirator brain, either complete or incomplete.

The characteristics of the Center 6 population were compared with those of the collaborative study, using chi square technique, in order to seek any possible differences which might decrease the validity of its use. Some significant differences were found. These are listed below together with an interpretation with regard to favorable, unfavorable, or irrelevant nature of the difference with respect to the specific problem of detailed analysis of presumptive brain death cases.

1. Significantly higher proportion of cases at age 19 or under ($p < .005$) - favorable, more representative of all age groups.
2. Significantly more Caucasians ($p < .01$) - irrelevant.
3. Significantly higher proportion of staff members conducting the first examination ($p < .005$) - favorable.
4. Significantly higher proportions of initial diagnoses as cerebral trauma and other ($p < .01$) - probably irrelevant.
5. Significantly higher proportion of cases with no drug intoxication ($p < .005$) - unfavorable but not critical for the objective.
6. Significantly higher number of EEG's reported ($p < .005$) - favorable.
7. Significantly higher proportion of cases showing ECS, no equivocal and no BA (biological activity) on an initial EEG ($p < .005$) - favorable.
8. Significantly higher proportion of patients who died after longer time interval from entrance ($p < .025$) - favorable for analyses of clinical course.
9. Significantly higher proportion of autopsy diagnoses of respirator brain ($p < .01$) and significantly lower proportion of diffuse cerebral damage ($p < .005$) - favorable and probably related to number 8.
10. Significantly higher use of high impedance on EEG's ($p < .05$) - unfavorable.

Thus, all differences are either insignificant or irrelevant except for item 10. On analysis it was found that the impedances for Center 6 were slightly above the median among the Centers. Consequently, this is not a serious difference.

RESULTS

A. General Findings on the Entire Population of the Collaborative Study.--In the presentation of results, we shall proceed from general groups to more specific categories. The initial presentation of data will relate to the total group of 503 cases of the collaborative study. This group necessarily included a number of conditions with varied outcomes, such as brain death as determined by current criteria, brain death as correlated with the existence of respirator brain, brain death as determined by attending physician evaluation, death from a variety of somatic causes, and survivors. It is possible, however, to relate clinical findings to the presence or absence of various criteria, to the final disposition, to the final outcome, and to the time course of examinations.

Although strenuous efforts were made to initiate examinations as early as possible after onset of coma and apnea, in practice it was not always possible to do so. The appearance of coma itself showed a considerable range in elapsed time following the timing of the initial cerebral disorder, as might be expected from the wide range of diagnostic entities. In the majority of cases, however, coma was prompt, with 66 percent occurring 1.9 hours after the cerebral insult. The remainder were distributed over a time ranging from 2 hours to greater than 2 days (table 1). Apnea tended to occur somewhat later since only 44 percent developed apnea in less than 1.9 hours after the onset of the cerebral insult. The elapsed time between development of the admission criteria, coma and apnea, and the first clinical examination can be estimated from timing of the initial EEG (table 2). In only 27 cases or 5.4 percent was this accomplished in less than 1 hour. Twenty-five percent were examined in less than 3 hours, 40 percent in less than 5 hours, and 61 percent in less than 12 hours. Thus, the majority of cases were examined by the standard procedures 5 hours or more after onset of apnea and usually of coma. During this time period, the clinical signs relevant to brain death may or may not have been present. Consequently, it is not possible to define the duration of clinical signs accurately in relation to the patient's course but only with respect to the initial examination.

Since extremes in body temperature and particularly hypothermia have been associated with brain death, body temperatures were compared to outcome and pathological findings (table 3). The technique of recording EEG's required normothermia and an unknown number of patients were kept on warming blankets. Consequently, the design of the study would tend to prevent observations being made at less than 90°F. The initial temperature showed no conclusive pattern with regard to outcome. No cases ultimately considered as brain death on currently accepted standards showed initial temperatures greater than 105°. There was a slight trend toward hypothermia in brain death cases, but the numbers involved were small (only 2 out of 114 being below 90°F. and only 19 or 16.7 percent being below 95°), and the values did not discriminate this group from other non-survivors. The survivors did show a relatively narrow range of temperature variations since none were below 90° or above 105°. Even when related to presence or absence of respirator brain, temperature level did not prove of discriminatory value (table 3). When the final temperature was compared with initial, no conclusive characteristics were noted, although there was a tendency toward hypothermia in the final readings with 21 percent being below 95° (table 4). Although falling blood pressure and vascular collapse has been noted as an index of brain death, only 16 percent of the series had systolic pressures less than 70 mm Hg on initial examination (table 5). Also less than one-fourth of the patients were administered vasopressor agents. The incidence of hypotension increased in the final examination but was still present in less than 25 percent.

The pulse rate also seemed to have little value in reflecting impending death in the series and only about 5 percent showed severe bradycardia on the final examination (table 6).

Pupillary sizes were divided into the following six groups:

Group 1 - pupils equal, 1 to 4 mm.
Group 2 - pupils equal, 5 to 8 mm.
Group 3 - pupils equal, greater than 8 mm.
Group 4 - pupils unequal and both less than 5 mm.
Group 5 - pupils unequal and both greater than 5 mm.
Group 6 - other combinations.

Consequently, Group 1 would be considered as small or normal and Group 2 as large and dilated. Group 3 is in the extreme range of dilation. For the entire group, pupils were about equally divided between large and small and did not change particularly in the final examination. There was, however, a difference in regard to outcome since 13 percent with Group 1 pupils survived, whereas, only 6 percent of Group 2 pupils survived. None survived in Group 3, but the total number was quite small (table 7). The ocular alignment was usually parallel with only 5 percent incidence of strabismus or skew deviations.

The pupillary reactions to light were preserved in 23 percent of the cases on the initial examination and with little change in incidence on the final examination. There was, however, a relationship of pupillary responses to outcome and EEG. When pupillary reactions were present on the initial examination, 21 percent of cases survived; whereas, when it was absent, only 4 percent survived (table 8). When the initial EEG was isoelectric, pupillary responses were absent in 98.4 percent of these cases. If the EEG showed biological activity, then pupillary responses were absent in only 60.4 percent of the cases (table 9).

A standard system of fundoscopy ratings was completed in 322 cases, of which 174 were abnormal. The most common abnormalities were (1) papilledema and (2) other findings (including hemorrhages). Sludging or segmentation of vessels was seen only in those with a fatal outcome; however, the total number was small (6.5 percent) and did not discriminate between those designated as brain death and other non-survivors (table 10).

All ten cephalic reflexes were absent on initial examination in 281 cases (56 percent) and the number absent increased on the final examination to 309 cases (61 percent). When the reflexes other than the pupillary response were assessed independently, they were each found to have been absent in about four-fifths or more cases on the initial examination. A slight tendency to recovery was noted on the final examination which was most evident in the audio-ocular response. It was also observed for pharyngeal, swallowing and cough reflexes. The ability to perform an adequate examination with unequivocal result varied greatly with the individual reflexes. Completion rates of examination were greatest with the following reflexes: pupillary, 99.6 percent; corneal, 99.6 percent; oculocephalic, 98.4 percent; audio-ocular, 97.6 percent; and snout, 97 percent (table 11).

In contrast to the cephalic reflexes, tendon reflexes were absent on the initial and final examination in less than half of the cases. They were slightly more often absent in the leg than in the arm (table 12).

Abdominal reflexes were absent in 92 percent of cases on the initial examination and did not change appreciably on the final. The plantar responses were absent in 65 percent on the initial examination and with little change on the final. When the plantar was present, there was a difference in the responses with the passage of time. When present on the initial examination, it was extensor in 54 percent; whereas, on the final examination, it shifted to predominantly flexor (63 percent). Muscle tone was absent on initial examination in about three-fifths of cases with a slight increase in the rate of absence on the final examination.

Spontaneous movements were present in only 10 percent of cases on initial examination and decreased on the final observation (table 13). Induced movements, however, were present initially in 27 percent with little subsequent change. Decerebrate or decorticate postures were present initially in 14 percent.

B. Correlations of Cephalic Reflexes, Spinal Reflexes, and Motor Findings With Electrocerebral Silence at Any Time Period (289 Cases).--In order to assess the validity of certain previously proposed criteria of brain death (such as absence of cephalic reflexes, absent spinal reflexes and absent somatic movement), it is necessary to compare the concordance of these test results with other indicators of brain death. In this and the following section, a series of increasingly rigorous operational and presumptive definitions of brain death are employed, against which the reflex results can be evaluated.

The first test involved the utilization of all cases from the total population of 503 individuals having the condition of coma, apnea and ECS at any given time in the study (table 14). There were 289 such cases. Some of these had subsequent return of biological acitivities (drug intoxication), hence the group is not a pure sample of presumptive brain death. The incidences of the reflex findings were tabulated for examinations conducted at 0 hours (the initial examination after entry), 12 hours, and the final examination. The latter could have occurred at any time from 0 hour to one week. The 12-hour group was smaller than the others due mainly to missed examinations and death.

On the initial examination, each of the cephalic reflexes were present at least once out of the total number of complete examinations which ranged from 247 to 282. In the cases of corneal and snout reflexes, these responses were present six times, and in the case of the jaw jerk seven times. By 12 hours, none was present except for the snout reflex (three times) and the jaw jerk (two times). On the final examination of patients still having ECS, positive reactions were found in all types of cephalic reflexes but at low incidence.

These data contrast sharply with the spinal stretch reflexes. One or more of these reflexes were present in 115 out of 283 cases (41 percent) at 0 hours, (51 percent) at 12 hours, and (43 percent) on the final examination. Reflexes in the upper extremities were more often present than those of the lower. Spontaneous movements were present at the three periods in 11-13 percent, while induced movements persisted in 15-18 percent.

Thus, cephalic reflexes were present rarely, spontaneous and induced movements occurred more frequently, and spinal reflexes were present in about one-half of these cases.

C. Incidence of Cephalic Reflexes, Spinal Reflexes, and Motor Findings in Presumptive Brain Death Cases Studied at Center 6.--From the 102 cases studied at Center 6, it was possible to select 63 cases fulfilling the criteria of coma, apnea, and ECS present for 24 hours or more. None of these cases survived. This group would, therefore, constitute a more stringent sample of presumptive brain death than the previous group (Section B) and would exclude drug intoxication and survivors.

Among these 63 cases, all cephalic reflexes were absent from the time of onset of the three criteria in 56 cases (table 15). One or more cephalic reflexes were present in seven cases throughout the 24-hour period. In examining individual reflexes, it was found that the snout reflex and the jaw jerk were most often persistent. The corneal, vestibular, and swallowing reflexes were present on either one or two occasions. In no instance was the light, oculocephalic, audio-ocular, pharyngeal, or cough reflex present.

The spinal stretch reflexes were reviewed in the 63 cases of presumptive brain death (table 16). In only eight cases were all tendon reflexes absent from the onset of the three criteria. In 55 cases, one or more reflexes were present. Persistence of reflexes was clearly not simply a function of the initial examination since the incidence persisted or even increased throughout the 24-hour period. In individual cases, it was found that the reflexes were either present early and disappeared late or were absent early and reappeared late. In many cases only one or two reflexes were present on either one or both sides of the body. They were, however, multiple in a significant number of cases, and even by 24 hours 19 cases showed three to five reflexes present. The individual reflexes present varied from case to case but biceps and triceps jerks were found more often than any other reflex.

The spinal reflexes were then subjected to an even more rigorous test of relationship to brain death. Cases were selected with coma, apnea, and ECS for 24 hours, no cephalic reflexes during this period, and a pathological diagnosis of definite brain death or respirator brain, either complete or incomplete. There were 18 such cases (table 17). In no case were the spinal reflexes completely absent throughout the 24-hour period. Again, the persistence of reflexes was not a phenomenon of early examination, but, in fact, showed a slight tendency to increase with time. In some cases, only one or two reflexes were present, but at the 24-hour period eight cases had three to five reflexes.

Spontaneous movements, induced movements and muscle tone were observed in the 63 cases having coma, apnea and ECS for 24 hours or more (table 18). While usually absent, it was remarkable that spontaneous movements were present in 14 cases and with a distribution throughout the time periods. Induced movements were found even more frequently, in 36 cases. Muscle tone was reported present in 25 cases with an even distribution throughout the time period. Again, these criteria were reviewed in relationship to the rigorous specification of brain death in the 18 cases also having loss of cephalic reflexes and pathological diagnosis of respirator brain (Table 19). Spontaneous movements were usually absent but were present in 2 out of 18 cases. Induced movements were more often present than not. Muscle tone was present in five cases.

The question of falling blood pressure was examined in the 63 presumptive brain death cases having coma, apnea and ECS for 24 hours (table 20). Recordings of systolic pressure below 80 mm Hg were made in only 25 instances in each of the time periods. There was no tendency for progressive hypotension.

D. Discrimination Indices of Individual Clinical Tests in the Comparison of Presumptive Brain Death With Non-Brain Death Cases. In the clinical diagnosis of brain death, it is not only necessary to identify clinical responses which are absent in brain death cases, but also to determine whether these responses may be present in non-brain death cases and have significant discrimination value between the two outcomes. For evaluation of these discrimination powers, results of individual tests were correlated with case outcomes in which brain death was defined as coma, apnea, and ECS for 24 hours or more, and were compared with cases having survival or cardiac death without ever developing ECS. For these analyses, pupil sizes were rated small (less than 2.5 mm), normal (2.5-5.5 mm), and large (5.5 mm or larger), and blood pressured was rated low (80 mm Hg systolic or less) and normal or above (more than 80 mm Hg). All other clinical tests were evaluated as absent or present. Correlations were computed for the 0, 6 and 24-hour examinations (table 21). It was found that large pupil size showed a positive correlation with presumptive brain death, but with low phi coefficients. Only at the 0 hour examination did the phi coefficient achieve a p value of $< .001$. Among other cephalic reflexes, absence of the following responses correlated well at 0 hour examination with presumptive brain death: light reflex at a coefficient of 0.502, oculocephalic at 0.556, and vestibular at 0.547. Other coefficients were positive but low. The audio-ocular and snout reflexes approached 0 correlation coefficient due to the fact that they tended to be absent not only in most cases of presumptive brain death, but also in cases of coma without this outcome. At 6 hours, the best correlations were found for: light reflex 0.626, corneal reflex 0.434, oculocephalic reflex 0.457, vestibular response 0.566 and swallowing reflex 0.481. At 24 hours, the best reflexes were: light 0.640, oculocephalic 0.423 and vestibular 0.540. Lowest coefficients were again found for audio-ocular and snout reflexes. Thus, the cephalic reflexes with the consistently greatest correlation coefficients were light, oculocephalic and vestibular.

Among the spinal reflexes, absence of the knee jerk showed fairly high correlations at 0, 6 and 24 hours with p values < 0.01 phi coefficients and other spinal reflexes never exceeded 0.378 and tended to decrease at 24 hours. Abdominal and plantar reflexes were without value in discrimination of the two groups. The discrimination indices for spontaneous and induced movements and tone were somewhat inconsistent at the three examinations but were fairly high in the case of spontaneous movements and tone at 0 and 24 hours. Low blood pressure correlated positively with brain death but at quite low coefficients.

E. Discrimination Indices for Selected Clinical Examinations Singly and in Combinations.--The following tests were selected for further statistical evaluations: pupillary light reflex, corneal reflex, oculocephalic response, vestibular response, knee jerk, spontaneous movements, induced movements and muscle tone. In these analyses, cases were limited to those in which complete data were available for all of the tests and time periods were extended to include 0, 6, 12 and 24 hours. In the first analysis, phi coefficients were computed for each examination period timed from the onset of the injury into the study, i.e., initial examination after onset of coma and apnea. With combinations of tests, such results were classified as all responses negative versus the condition of one or more present. Highest discriminative values were still found most consistently for pupillary light and vestibular reflexes, either alone or in combination, followed by spontaneous movement, oculocephalic response, and corneal reflex (table 22). The best combinations of 3 tests were pupillary light, oculocephalic and vestibular reflexes and pupillary light, vestibular reflex and spontaneous movements.

Since the onset of ECS probably corresponds best with the time of onset of brain death, these cases were then compared in another way. Cases with presumptive brain death had initial examination time adjusted to begin at the onset of ECS; whereas, those with other outcomes were timed from the onset of initial examination after entry into the study (table 23). In this evaluation, pupillary light and vestibular reflexes still showed highest correlation coefficient followed by oculocephalic reflex, muscle tone, corneal reflex and spontaneous movement. The dual combination of pupillary light and vestibular reflexes showed highest values. The combination of 3 with highest values were pupillary light, corneal and vestibular reflexes; pupillary light, oculocephalic and vestibular reflexes; and pupillary light, vestibular reflexes and spontaneous movements.

F. Frequency of Cephalic Reflexes in Normal Persons and Hospitalized Patients.--Most of the cephalic reflexes are considered to be present in all normal individuals. The experience of the clinical examiners, however, indicated that several reflexes are frequently absent but that the normal incidence is unknown (11, 12). Consequently, a survey was made of 79 normal individuals between the ages of 3 and 63 years and 46 hospitalized patients (table 24). It was found that the audio-ocular reflexes could regularly be obtained in all of the 79 normal subjects except two in whom repeated examinations showed absence of response. No neurological deficit could be identified in these two subjects. The snout reflex was frequently absent (65 absent out of 79) and the jaw jerk was occasionally absent (12 cases). Groups of alert patients and drowsy or post-anesthetic patients were examined by the same team of neurologists who participated in the brain death study. In alert patients audioocular reflexes were present in all but a few instances; whereas, the other two reflexes were often absent. The low incidence of jaw jerk may either reflect the difference in hospitalized patients from normal subjects or variation in examiner detection rate. No remarkable difference was noted in the drowsy patients. Consequently, both snout and jaw reflexes as determined by a group of representative neurologists in a hospital situation are frequently absent in subjects without neurological disease.

G. Predictive Value of Clinical Criteria Relationship to Pathological Diagnosis.--In the 102 cases of Center 6, only 6 cases were encountered which fulfilled the Harvard criteria of coma, apnea, ECS, dilated pupils, absence of cephalic reflexes, absent spinal reflexes, absent movement and absent tone for 24 hours. No autopsies could be obtained in any of these cases.

The predictive value of the condition of coma, apnea and ECS for 24 hours or more was then evaluated in 27 cases in which autopsies were completed. In 22 instances, complete or incomplete respirator brain was diagnosed by the Center 6 neuropathologist (Leopold Liss, M.D.). In two cases, questionable or early respirator brain were recorded, one in a subject with intracerebral and intraventricular hemorrhages with secondary brain stem hemorrhages, and the other in a case of severe cerebral edema and tonsillar herniation following surgical removal of a massive intracerebral hematoma. In 3 cases, respirator brain was not diagnosed, but there were secondary brain stem hemorrhages in each. Brain trauma was present in two cases, and primary intracerebral hemorrhage in a third.

The relationship was then assessed by the following set of conditions present for any duration: coma, apnea, ECS and absence of all cephalic reflexes except the snout and jaw reflexes. There were 35 such cases in which autopsies were completed. In 27 cases, a positive diagnosis of respirator brain, either complete or incomplete was made. Two questionable or early respirator brains were diagnosed. Respirator brain was considered not to be present in 6 cases. All of these had secondary brain stem hemorrhages resulting from herniation syndromes with the following neuropathological diagnoses: brain trauma 3, intracerebral and intraventricular hemorrhage 1, intracerebral hemorrhage 1, and meningitis with multiple cerebral abscesses 1. Thus, these criteria, present at any time in the sequence of observations, were associated either with pathological diagnosis of respirator brain or a destructive process accompanied by brain stem hemorrhages.

H. Temporal Course of Clinical Signs in Presumptive Brain Death, Drug Intoxicated Survivors and Non-Drug Intoxicated Survivors.--In the expectation that major differences in patterns might be found, time courses of clinical signs were plotted for presumptive brain death cases and survivors in periods from 0 to 72 hours after entry into the study.

All of the 44 surviving patients from the major collaborative study were divided into drug-related and non-drug-related causes. On the first examination, there were 25 drug intoxicated survivors, and as some of these gradually recovered, they left the examination sequence, until by 48 hours 12 remained. Of the non-drug-related survivors, there were 19 at entry and 6 at 48 hours. A minor artifact in the plotting of survivor scores was caused by the examination protocol. Cases showing a return of respirations or consciousness were switched to a 24-hour examination schedule; hence, cases improving at 12 hours would next be reported at 36 hours rather than at 24. Consequently, 24-hour cases are weighted toward greater severity of disorder (less positive responses), and the 36-hour cases toward lesser severity (more positive responses).

Temporal patterns of the drug intoxicated survivors are plotted in figures 1 through 5. Electrocerebral silence was uncommonly present (one case at 0 hours and two at 6 hours) and was not present beyond 24 hours. The incidence of spontaneous respirations rose quite sharply until it was present in 67 percent of the cases at 12 hours, and 93 percent by 48 hours (figure 1). The percent with cerebral responsivity rose steadily and less rapidly.

In plotting pupil size (figure 2), it was considered that 2.5 to 5.5 mm constituted the normal range within the usual illumination of a hospital environment (13). Less than 2.5 mm was considered small and greater than 5.5 mm large. It has already been observed that no survivor had pupils in the extreme range of dilation, greater than 8 mm. It was expected that intoxication including certain drugs such as atropine or glutethimide would be associated with large pupils, while opiates would be associated with small. Presumably reflecting the predominating intoxication with barbiturates (14), 61 percent of pupils examined were within the normal range at 0 hour and 55-81 percent later.

Pupillary light reflexes were present at high incidence on entry (71 percent with further increase with time (figure 3). Corneal reflexes were present at only 32 percent on entry, but rose rapidly to 93 percent by 48 hours. The group of pharyngeal, swallow, and cough responses were remarkable in that all were present at about 15 percent initially, but returned at rapid rates to about 90 percent by 72 hours (figure 4). The jaw jerk and snout reflexes departed from the course of other responses, remaining at quite low incidence throughout the 72-hour period. Tendon reflexes, muscle tone, and induced and spontaneous movements followed a rather similar pattern with slow rates of return (figure 5).

The non-drug-related survivors were characterized in general by much greater variability of temporal patterns and by generally delayed return of responses in comparison with drug intoxication. The incidence of spontaneous respirations did rise sharply to 54 percent by 6 hours, but then showed little change over the ensuing 42 hours (figure 6). Pupil size was quite variable with 32 percent enlarged on initial examination, and with over 50 percent being small (figure 7). With time, there was a slow approach to the normal range. Among the cephalic reflexes, the light, corneal, oculocephalic and vestibular responses were present initially at about 50 percent level and showed irregular return to 100 percent by 72 hours (figure 8). Audio-ocular and pharyngeal reflexes were absent in almost all patients on entry, but returned gradually over 72 hours (figures 8 and 9). Induced movements were present initially at a rather high incidence (62 percent) and steadily increased after 6 hours (figure 10). Other reflexes behaved erratically.

Striking differences were noted in the temporal pattern of patients with presumptive brain death defined as coma, apnea, and ECS for 24 hours or more. Among these 63 cases, electrocerebral silence was present in 74 percent on initial examination and reached 100 percent by 72 hours (figure 11). Spontaneous respirations and cerebral responsiveness were rarely present, and remained at 0 incidence from 48 hours on. With regard to pupil size, it was observed in the total population of the collaborative studies that no survivor had pupils in the extreme range of dilatation greater than 8 mm. On the other hand, it is evident that not all cases of presumptive brain death have pupils dilated beyond 5.5 mm (figure 12). Pupils within normal range varied between 25 and 40 percent, and there was no major change with time. The pattern of cephalic reflexes differed markedly from that of the survivors (figures 13 and 14). All were present in low incidence, well below 10 percent. None showed any definite recovery and most tended to approach 0 at some point between 24 and 72 hours. Some exceptions with late persistence at low incidence included corneal, swallow and jaw reflexes. Spinal reflexes were decidedly different (figure 15). Stretch reflexes were present initially in about 50 percent of cases and did not fall off with time, but, rather, tended to increase. A similar pattern was noted for induced movements. Spontaneous movements were present in low incidence and showed little tendency to change.

The marked differences in patterns between findings in presumptive brain death and the two groups of survivors are displayed in figure 16. Spontaneous respirations, pupillary light reflex, pharyngeal reflex and corneal reflex have markedly different time course in brain death as compared with survivors.

I. Quality of Survivors.--The collaborative study required a 3-month followup examination on patients who were entered into the study but survived. Since apnea was an entrance criterion, it is not surprising that of the 503 patients entered, only 50 (10 percent) survived the acute stage. Of these,six died prior to the 3-month followup examination prescribed by the study protocol.

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Twenty-seven of those alive initially had entered the study with primary diagnosis of drug intoxication. Three of these were lost to followup and therefore 3-month progress reports were obtained on 24. The other 17 survivors had diagnoses similar to those observed in fatal cases. Table 25 expresses the distribution of diagnostic categories by outcome. Absolute numbers in all categories are probably too small to be conclusive. However, it seems clear that all but one of the drug intoxication patients were completely recovered. Of the other diagnostic categories, complete recovery at three months was reported in only two cardiac arrest patients and in one stroke patient. The two cardiac patients recovered rapidly, regaining spontaneous respirations within 6 hours of onset. Since the cerebrovascular disease patient recovered completely from coma, apnea and all other neurological deficits within 13 hours, his disease was classified as transient cerebral ischemia in the vertebral basilar system.

No absolute correlations can be made, therefore, between the fact of survivorship or its quality and any of the other parameters measured in the study. Although 27 patients with primary diagnosis of drug intoxication survived, 9 died; while 100 patients with global cerebral ischemia caused by primary cardiac arrest died, 5 survived.

There were survivors in each major category and in each decade of the age distribution.

Patients proceeding to complete or nearly complete recovery began that trend very early in their course (figure 16). Among the survivors, apnea persisted for less than 6 hours in 12, less than 12 hours in 21. Of 12 cases apneic for more than 24 hours, half were drug cases, all of whom made complete recoveries, while the other six made poor recoveries.

All of the survivors had biological activity in each of their EEG's except two patients who were drug intoxicated. These two patients constitute the only instances in the entire study in which the combination of unresponsive coma, apnea, absent cephalic reflexes and ECS failed to forecast imminent death. Neither had dilated pupils, however.

J. Special Features in Patients with Cerebral Ischemia Secondary to Cardiac Arrest.--Approximately 20 percent of the study group had sustained an encephalopathy due to cardiac arrest without primary central nervous system disorder. Another 10 percent had a cardiac arrest complicating their primary central nervous system insult. Five of the survivors had a primary diagnosis of cerebral ischemia due to cardiac arrest. It seemed worthwhile to examine some details of the clinical findings and courses of these cases since they might differ from the patterns of brain death secondary to primary cerebral disorder. Inspection of results from the entire study did not suggest any characteristic patterns for cerebral ischemia. Consequently, 15 cases of patients with primary diagnosis of cerebral ischemia secondary to cardiac arrest were analyzed from the center 6 group. Only one of these patients survived, two having been declared brain dead and the remaining 12 designated as cardiac deaths. Detailed data on the other 4 survivors of cardiac arrest from the general study were also available for analysis.

First, a group of these patients having developed ECS were selected out for scrutiny. There were 10 such cases. It was remarkable that pupils were dilated in most of these cases. None were less than 2.5 mm at any examination. Pupil size greater than 5.5 mm was noted in 80 percent at 0 hours, 90 percent at 6 hours and 100 percent at 12 hours. All of the cephalic reflexes were absent at 0, 6, 12, 24 and 48 hours, except for the pupillary light reflex which was present in a single case at 6 hours and the snout reflex and jaw jerks which were present at 10 percent and 12.5 percent respectively at 0 hours with variable incidence thereafter. Tendon reflexes were present at rates between 10 and 44 percent during the first 24 hours. Muscle tone was present in 10 percent and spontaneous movements in 20 percent at 0 hours. Consequently, with the exception of uniform development of dilated pupils, the pattern of findings does not differ from that of presumptive brain death cases in general.

Nine cases were then considered in which the patients either survived or never developed ECS. A clinical pattern contrasted sharply with the above cases. Pupils did not tend to be dilated as frequently as in cerebral death cases since at 0 hours 22 percent were greater than 5.5 mm, 11 percent were in the normal range and 66 percent were smaller than 2.5 mm. By 24 hours none was dilated and by 48 hours 75 percent were in the normal range. At 0 hours the incidence of some of the cephalic reflexes present were as follows: pupillary light 55 percent, corneal 44 percent, oculocephalic 33 percent and vestibular 66 percent. The audio-ocular was 0 as were pharyngeal and cough. The pupillary light response returned to 100 percent incidence by 12 hours and the incidence of pharyngeal, swallowing and cough reflexes also increased appreciably by this time. Most of the other reflexes fluctuated irregularly in sequential examinations. The stretch reflexes were present at 88 percent at 0 hour and ranged between 66 and 75 percent thereafter. The pattern was therefore very similar to those of the nondrug intoxicated survivors previously analyzed.

In view of the possibility that the systemic blood pressures might differ in cardiac arrest cases with ECS as opposed to cases of cardiac arrest without presumptive brain death, the systolic and diastolic pressures of the center 6 patients with cardiac arrest were examined.

Ten cases of cardiac arrest with ECS were compared with four having biological activity (table 26). The mean values for systolic and diastolic pressures were compared at various time intervals after entry into the study ranging from 0 hours to 48 hours. The mean values of blood pressures were consistently lower at each time interval in cases with ECS as compared to those with biological activity. The numbers analyzed were small and the standard deviations were large, and significance was not approached except for systolic pressures at the 12-hour examination ($p < 0.05$) and at 6 hours ($p < 0.1$). Examined in another way, it was noted that none of the cases with biological activity had systolic pressures of 80 mm or less at 0 hour and 6 hours. At 12 hours one out of the four had a systolic pressure of 80 and at 24 hours one had a systolic pressure of 80. At 48 hours all exceeded this level. Among those with ECS, values of systolic pressure of 80 or less were found in 6 out of 10 cases at 0 hours, 5 out of 9 at 6 hours, 5 out of 9 at 12 hours, 4 out of 7 at 24 hours and 1 out of 4 at 48 hours.

K. Special Features in Primary Brain Stem Lesions.--In the center 6 group of cases, there were three patients having primary brainstem hemorrhages in whom an autopsy was performed. Two were part of the major collaborative study while one was a part of the modified study. All three were males of ages 54, 67 and 50.

In all three cases, there occurred the coexistence of coma, apnea and absence of cephalic reflexes on one or more examinations in which biological activity was present on the EEG. This was observed on two examinations in one case, two in another, and on one examination in a third. In the latter case, that in the modified study, only pupillary and corneal reflexes were tested in the cephalic group. In one case, respirations returned on the last two examinations. In another, biological activity on the original EEG changed to ECS on the last two recordings. All cases died of cardiac arrest.

On pathological examination, the case with persisting coma and absence of all cephalic reflexes for 36 hours but with return of respirations in the last 24 hours, showed only a primary brainstem hemorrhage. In the case with coma, apnea and absence of pupillary and corneal reflexes for 36 hours with shift of initial biological activity on EEG to ECS for 24 hours, pathological examination showed both a primary hemorrhage in the midbrain and pons and changes of respirator brain. In the case with coma, apnea and absent cephalic reflexes on the 24-hour examination but with persisting biological activity, pathological examination revealed a midbrain hemorrhage and incomplete respirator brain. Consequently, it appears that the triad of coma, apnea and loss of cephalic reflexes need not always be associated with respirator brain but can occur in some instances of primary brainstem lesions.

DISCUSSION

The time course of changes in the incidence of clinical findings is of value in separating out various major diagnostic entities in patients initially presenting with coma and apnea. Particular differences were noted with respect to survivors of drug intoxication as compared with those cases which progressed to coma, apnea and ECS for at least 24 hours. Among the drug cases, the pupillary light reflex was present at high incidence on the initial examination and steadily increased. There was a sharp rise in the incidence of spontaneous respirations and corneal reflex within the first 12 hours and pupil size was normal in over 80 percent. The return of pharyngeal, swallowing and cough responses occurred at a slightly longer time scale. In contrast, the presumptive brain death cases with coma, apnea and ECS for 24 hours or more retained cephalic reflexes in low incidence on initial examination and this incidence remained low or approached 0 in subsequent examinations at 24 and 48 hours. Therefore, in cases when the possibility of drug intoxication is considered but is in doubt, continued observation for 12 hours or more will usually clarify the issue.

The absence of the cephalic reflexes generally correlates well with the development of coma, apnea and ECS; however, there are some considerable variations among the individual reflexes. Dilation of the pupil has been considered a sign of cerebral death; however, it was not always present in our presumptive brain death cases. Moreover, the phi coefficient of pupil size in distinguishing brain death from cases without this condition proved to be relatively weak. On the other hand, the pupillary light, corneal, oculocephalic and vestibular reflexes were present only rarely in presumptive brain death cases and displayed relatively high phi coefficients. The audioocular reflex, on the other hand, proved to be of very little value in diagnosis. It was, indeed, absent in cases of brain death, but it was also absent in individuals who survived. It was found rarely to be unelicitable in normal subjects and frequently so in drowsy patients. Consequently, it appears excessively sensitive and has a very poor discriminative value. The jaw and snout reflexes were noted to be persistent, more than other cephalic responses, in the Center 6 cases having coma, apnea and ECS for 24 hours or more. Furthermore, in the major collaborative study, the snout reflex was present in 3 out of 135 cases examined at 12 hours after the onset of ECS and the jaw jerk in 2 such cases; whereas, none of the other cephalic reflexes were present at that time. This rare but definite persistence may possibly be related to the occasional survival of short latency monosynaptic components of these reflexes which might well occur with the sparing of only the lateral rim of the pons and midbrain with the short connection between fifth and seventh nerve muclei for the snout reflex and the fifth nerve components for the jaw jerk. Presumably the technique of examination would not have distinguished between the monosynaptic component and the nociceptive bilateral polysynaptic component which would require a wider distribution of neural connections in the brain stem including central core of the tegmentum and ventral areas (15, 16). Furthermore, it was noted that the jaw and snout reflexes tend to remain at low incidence even in drug survivors during their recovery period. The snout reflex may be absent in normal persons or hospitalized patients and occasionally the jaw jerk is not present. All of these factors evidently contributed to the low correlation coefficients of these two responses. The pharyngeal, swallowing and cough reflexes had rather variable discrimination indices but they did prove to be of great value in the sequential examination of drug intoxication.

With respect to the tendon reflexes, presence or absence of these responses bears little relationship to the identification of brain death. This was demonstrated by several tests. First, in examining patients with coma, apnea and ECS for 24 hours or more among the Center 6 group, one or more tendon reflexes were present in all but 8 of 63 such cases. The total incidence persisted or even increased in time. Secondly, with the strict criteria of brain death consisting of coma, apnea and ECS for 24 hours, absence of cephalic reflexes for 24 hours, and diagnosis of respirator brain at autopsy, tendon reflexes were absent in none of these 18 cases, nor was there any tendency toward a progressive decrease with time. Third, in estimating the predictive value of the tendon reflexes in relation to the development of coma, apnea and ECS for 24 hours or more, low discrimination coefficients were found at any of the times tested, with the single exception of knee jerk, and the coefficients tended to decrease with late examination. Fourth, in the major collaborative study one or more tendon reflexes were retained in 114 out of 262 cases on the final examination. Consequently, it is concluded that the spinal reflex arc may be preserved with cerebral death, probably as a reflection of frequent independent survival of the spinal cord with its separate blood supply. This conclusion is consistent with the recent findings of Jorgensen (9). Consequently, the spinal tendon reflexes should not be used as clinical criteria.

The plantar responses proved to be of no value in recognition of brain death, confirming the original assertion of Mollaret and Goulon (1). They were present in 66 out of 289 cases in the major study on final ECS examination. There was a tendency for these reflexes to be extensor initially and flexor on the final examination. The abdominal reflexes also proved to have no discrimination value.

In terms of movement, it was noted that spontaneous movements have some value in that their absence correlates with the outcome of brain death but with relatively weak phi coefficients. Furthermore, spontaneous movements were noted in 2 out of 18 cases with our rigorous definition of brain death. Induced movements were present more often than not in patients with this rigorous definition and they displayed generally low phi coefficients at the three examination intervals tested. Muscle tone proved to be of better value than induced movement, but tone was still present in 5 out of 18 cases with the rigorous definition of brain death. The phi coefficients were fairly good with values of 0.337 at 6 hours and 0.544 at 24 hours. It was concluded, then, that induced movements and tone need not be used in the diagnosis of brain death and the requirement of their absence would exclude a significant number of cases. The retention of spontaneous movements would doubtless exclude a small number of brain death cases. These movements were not voluntary responses but were fragmentary movements which could not be identified by the examiners as recognized reflex patterns. Use of such movements as clinical criteria would be principally for reasons of lay interpretation.

Body temperature was of distinctly limited value in discriminating any group during early phases of observation. The only exception involved cases of drug intoxication inasmuch as no survivor ever had a temperature below 90°F. It is recognized that poikilothermia has regularly been observed in brain death cases after resuscitative efforts were maintained for several days (9).

Likewise, blood pressure was of very little diagnostic value. There was no evidence of hypotension as a useful criterion for brain death. Systolic blood pressure below 80 mm Hg occurred on any one examination in less than one half of cases with coma, apnea and ECS for 24 hours or more. There was no tendency toward a progressive drop in blood pressure. Low correlation coefficients were found for blood pressure with the development of coma, apnea and ECS for 24 hours on examinations at 0, 6, and 24 hours. Consequently, it is concluded that control of the systemic blood pressure in the horizontal position is generally maintained adequately even in brain death.

The tendency toward lower blood pressures in cardiac arrest cases with ECS than those with biological activity is of borderline significance but is suggestive of a role of prolonged relative hypotension in intensifying brain damage in the ischemic brain with pressure dependent flow.

Conversely there is the hint of a protective effect of barbiturate in some survivors. Two of the drug intoxicated patients recovered without deficits despite cardiac arrests during their hospital course. Two of the cases of primary cardiac arrest had measurable, althought low levels of barbiturate in their blood samples. Another two cases were complicated by seizures which were treated with barbiturate medications. These six cases represent the spectrum over which various doses and time sequences of barbiturate admistration might modify a coexisting primary or secondary cerebral insult. The recently reported protective effect of these drugs in animal models of global and focal cerebral ischemia require special attention in relation to the problem of brain death (17, 18). By reducing cerebral oxygen consumption and demand, barbiturate agents reduce cerebral blood flow through the autoregulatory mechanism. Once barbiturate concentrations depress respiration, the resultant hypercapnia could cause increased cerebral flow (19). One might speculate upon several ways in which unsuspected barbiturate drugs might modify the clinical picture and physiological measurements obtained in cases of head injury or cardiac arrest. The very agents which might increase cerebral tolerance to anoxia and ischemia could also lead to erroneous judgements based upon EEG or cerebral blood flow measurements.

In conclusion, some of the previously proposed clinical criteria for brain death have not been substantiated in this study (20). Thus, the absence of spinal stretch reflexes should not be required. The audio-ocular response is too sensitive and the snout and jaw jerks may be retained in brain death; therefore, all three of these should be deleted. Plantar responses and abdominal reflexes are of no value. Muscle tone and induced movements are often present in brain death and hence are of very limited usefulness. Hypothermia and falling blood pressure do not occur regularly and need not be considered as a criteria for brain death. Some clinical tests which have been considered of value are listed in t able 27 and are recommended for use in combination with the demonstration of ECS. These include: cerebral unresponsivity (coma), absence of spontaneous respirations, pupillary light reflex, vestibular reflex, oculocephalic reflex and corneal reflex. Some of these have been included on the basis of very high discriminative power, others because of the value of their early return to normal in survivors, others on account of compelling reasons of lay interpretation of death, and others because of high examination completion rates. Spontaneous movements are included as probable or optional. The pharyngeal, swallowing, cough reflexes, and the pupil size need not be used as required criteria in brain death determination, but are quite useful in the identification of drug intoxicated or other survivors.

Our data indicate that the coexistence of coma, apnea and loss of the above responses will usually predict cerebral death but will allow for some errors to be made in occasional cases with primary brain stem lesions and in a few instances of drug intoxications or other potential survivors. The additional criterion of ECS eliminates such errors according to the present study. Our data indicate that even with all of these criteria, there will be some failures in pathological correlations, usually in the cases of severe or massive cerebral lesions but without evidence of respirator brain. It is probable that the above criteria have been analyzed as far as is possible to do so. Further accuracy in diagnosis will very likely rely upon another instrumental technique relating to the basic pathology of capillary flow failure, such as the assessment of cerebral blood flow by isotope methods (21, 22).

Finally, the time necessary for duration of clinical criteria in identifying brain death has not yet been accurately defined. The presence of the above criteria on any examination should not be construed to indicate that brain death may be predicted by the concurrence of criteria for the period of an examination (usually 30 to 60 minutes). On the contrary, the time of the initial examination did not relate in any precise way to the time of onset of brain death. Under the circumstances of this study, from 1 to 6 hours could have elapsed prior to the initial examination. Hence, the condition of coma, apnea, ECS and loss of cephalic reflexes and spontaneous movement could have been present for several hours by the time of the completion of the initial examination.

SUMMARY

Clinical examination data have been analyzed in the 503 cases of the collaborative study and, with regard to detailed statistical analyses, in 102 cases of the Center 6 group.

The incidence of positive or negative findings have been compared for:

1. Groups in the total study classified as brain death and as cardiac death, by attending physician opinion.
2. Cases in the major study having ECS on first, 12 hour and final examination.
3. Center 6 cases having coma, apnea and ECS for 24 hours, and
4. Center 6 cases having these criteria with loss of cephalic reflexes and a pathological diagnosis of respirator brain.

Correlation coefficients have been computed for each clinical test in relationship to the comparison of various groups. The time course of clinical findings has been compared for drug intoxication, non-drug intoxicated survivors, and presumptive brain death cases. Special features of cardiac arrest encephalopathies and primary brainstem lesions have been examined.

It is concluded that the presence or absence of spinal stretch reflexes is of no value in the identification of brain death.

Induced movement (brainstem and spinal polysynaptic reflex responses) can be present in cases identified as brain death and their absence is of weak discriminative value. Absence of muscle tone is also of limited discriminative value but absence of spontaneous movements has slightly greater diagnostic value.

Pupillary size is also a rather weak predictor but is helpful in the sequential analysis of suspected cases and the differentiation of drug intoxications.

Absence of cephalic reflexes generally correlates well with the presence of brain death, but some reflexes are of more importance than others. Those of greatest value include pupillary light, corneal, oculocephalic, and vestibular reflexes. Snout reflex and jaw jerk may be absent in some normal persons and are the two cephalic reflexes most likely to persist in brain death cases. The audio-ocular reflex is absent in brain death but is excessively sensitive, being absent in other cases with coma and apnea. Pharyngeal, swallowing and cough reflexes are weak discriminators but have a value for sequential study in the identification of drug intoxication and for lay interpretation.

Abdominal and plantar reflexes are of no value. Blood pressure, pulse and temperature show no characteristic pattern in the differentiation of brain death from other conditions in this study.

Since spontaneous movements may have considerable significance to relatives and lay observers, it may be desirable to retain these. Consequently, absence of the following responses should be used as clinical criteria for brain death in addition to coma, apnea and ECS: pupillary light reflex, corneal reflex, oculocephalic reflex, vestibular reflex and spontaneous movements.

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Table 1

Elapsed Time From Cerebral Insult to Cerebral Unresponsiveness

Elapsed Time	Total number (percent) of cases
1.9 hrs.	333 (66.2)
2-3.9	22 (4.4
4-7.9	13 (2.6)
8-15.9	10 2.0)
16-31.9	23 (4.6)
32 hrs. to 2 days	11 (2.2)
2 days	58 (11.5)
Unknown	33 (6.6)
TOTAL	503

Table 2

Elapsed Time Between Beginning Artificial Respiration or Apnea, Whichever Was Later, and the Start of the Initial EEG

Elapsed Time	Total Number of Cases (percent)
0-0.9 hours	27 (5.4)
1-1.9	48 (9.5)
2-2.9	53 (10.5)
3-3.9	45 (8.9)
4-4.9	30 (6.0)
5-11.9	103 (20.5)
12+ hours	186 (37.0)
Unknown or No EEG	11 (2.2)
TOTAL	503

Table 3

Relationship of Initial Rectal Temperature to Outcome and Status of Brain

		Outcome No. Observed (No. expected on basis of chance alone)			Respirator Brain in Autopsy Cases	
Rectal Temperature °F	No.	Cardiac Death	Brain Death	Survivors	Yes	No
Unknown	7	5 (4.8)	2 (1.6)	0 (0.6)	1	0
<90	12	10 (8.2)	2 (2.7)	0 (1.0)	5	2
90-94.9	55	32 (37.7)	17 (12.5)	6 (4.8)	11	14
95-99.9	265	170 (181.8)	68 (60.1)	27 (23.2)	44	74
100-104.9	156	120 (107)	25 (35.4)	11 (13.6)	30	43
>105	8	8 (5.5)	0 (1.8)	0 (0.7)	0	2
TOTAL	503	345	114	44	91	135

Table 4

Temperature, Initial and Final Examinations

°F	Number of Cases Initial	Final
90 or unknown	19	22
90-94.9	55	84
95-99.9	265	252
100-104.9	156	140
105	8	5
TOTAL	503	503

Table 5

Systolic Blood Pressure, Initial and Final Examinations

	Number of Cases	
Systolic Pressure	Initial	Final
< 50	45	78
50-69	38	47
70-89	103	100
90-109	125	119
110-129	84	94
130-149	47	30
150-169	28	20
170-189	15	10
190-209	5	2
>210	13	3
TOTAL	503	503

Table 6

Pulse Rate, Initial and Final Examinations

Beats/Minute	Number of Cases Initial	Final
<50	9	25
50-69	48	60
70-89	123	121
90-109	147	150
110-129	109	96
130-149	45	31
>150	22	19
TOTAL	503	503

Table 7

Size of Pupils, Initial and Final Examinations

		Number of Cases		
Size of Pupils		Initial	(% Survivors)	Final
Equal	1-4 mm	180	(13)	185
	5-8 mm	194	(6)	181
	>8 mm	7	(0)	7
Unequal both	<5 mm	36	(11)	29
	>5 mm	37	(3)	46
Other		45	(2)	45
Unknown		4		9
TOTAL		503		503

Table 8

Pupillary Reaction to Light, Initial and Final Examinations

	Number of Cases		
Reaction	Initial	(% Survivors)	Final
Pupillary Reaction Absent	384	(4)	385
Pupillary Reaction Present	117	(21)	112
Pupillary Reaction Other or Unknown	2	(0)	6
TOTAL	503		503

Table 9

Relationship of Initial EEG Findings to Initial Pupillary Responses

EEG Results	Total	Pupillary Responses Absent	Present	Not Examined
ECS	187	183	3	1
Equivocal	30	28	1	1
BA	283	171	112	--
TOTAL	500*	382	116	2

*Three cases of the 503 total had no initial EEG.

Table 10

Relationship of Ophthalmoscopic Examinations, Findings and Outcome

Findings	Total	Cardiac Death	Brain Death	Survivors	Unknown
Normal	148	89	19	32	8
Pallor	20	4	8	8	--
Papilledema	55	31	24	--	--
Sludging	21	19	2	--	--
Other	78	53	14	9	2
Total Examined	322	196	67	49	10
Not Done	129	65	26	30	8
TOTAL	451				

Table 11

Cephalic Reflexes, Initial and Final Examinations

Reflex		Initial-Number of Cases (%)	Final-Number of Cases (%)
All Absent		281 (55.9)	309 (61.4)
Pupillary	Absent	384 (76.3)	385 (76.5)
	Present	117 (23.3)	112 (22.3)
	Other	2 (0.4)	6 (1.2)
Corneal	Absent	411 (81.7)	387 (76.9)
	Present	90 (17.9)	110 (21.9)
	Other	2 (0.4)	6 (1.2)
Oculocephalic	Absent	432 (85.9)	415 (82.5)
	Present	63 (12.5)	71 (14.1)
	Other	8 (1.6)	17 (3.4)
Vestibular	Absent	391 (77.7)	374 (74.4)
	Present	68 (13.5)	62 (12.3)
	Other	44 (8.7)	67 (13.3)
Audio-Ocular	Absent	486 (96.6)	450 (89.5)
	Present	5 (1.0)	39 (7.8)
	Other	12 (2.4)	14 (2.8)
Snout	Absent	465 (92.4)	459 (91.3)
	Present	23 (4.6)	29 (5.8)
	Other	15 (3.0)	15 (3.0)
Pharyngeal	Absent	398 (79.1)	384 (76.3)
	Present	26 (5.2)	56 (11.1)
	Other	79 (15.7)	63 (12.5)
Swallowing	Absent	393 (78.1)	379 (75.3)
	Present	25 (5.0)	55 (12.5)
	Other	85 (16.9)	61 (12.1)
Cough	Absent	407 (80.9)	391 (77.7)
	Present	24 (4.8)	55 (10.9)
	Other	72 (14.3)	57 (11.3)
Jaw Jerk	Absent	440 (87.5)	441 (87.7)
	Present	39 (7.6)	47 (9.3)
	Other	24 (4.8)	15 (3.0)

Table 12

SPINAL REFLEXES, INITIAL AND FINAL EXAMINATIONS

		Examination	
Muscle Tone (N=503)		**Initial Number of Cases**	**Final Number of Cases**
All absent		325	367
Arm			
	Absent	347	381
	Present	151	115
	Other	5	7
Leg	Absent	342	376
	Present	159	121
	Other	2	6
Superficial Reflex (N=503)			
All absent		305	315
Abdominal			
	Absent	461	440
	Present	17	31
	Other	25	32
Planter			
	Absent	326	335
	Present	173	162
	Extensor	94	60
	Flexor	79	102
	Other	4	6
Tendon Reflex (N=503)			
All absent		243	247
Arm			
	Absent	267	270
	Present	234	227
	Other	2	6
Leg			
	Absent	326	309
	Present	173	187
	Other	4	7

Table 13

Motor Activity, Initial and Final Examination

Type		Initial Number of Cases	Final Number of Cases
All Absent		288	303
Spont. Mov.	Absent	362	368
	Present	51	24
	Other	90	111
Induced Mov.	Absent	362	351
	Present	138	144
	Other	3	8
Abn. Posture	Absent	435	470
	Present	68	33
	Other	0	0
TOTAL		503	503

Table 14

INCIDENCE OF POSITIVE REFLEXES AND MOTOR FINDINGS IN 289 CASES HAVING ELECTROCEREBRAL SILENCE AT ANY TIME IN THE COURSE OF OBSERVATION

	0 hour		12 hours		Final	
Clinical Test	No. of Cases Positive	No. of Exams Completed*	No. Pts.	No. Compl.	No. Pts.	No Compl.
Pupillary light reflex	5	282	0	131	4	261
Corneal reflex	6	282	0	131	4	261
Oculocephalic response	3	281	0	131	2	260
Vestibular reflex	2	270	0	130	0	252
Audio-ocular reflex	1	279	0	131	0	261
Snout reflex	6	281	3	131	1	260
Pharyngeal reflex	3	250	0	120	2	243
Swallow	3	247	0	120	1	242
Cough	3	253	0	120	2	244
Jaw jerk	7	279	2	129	2	260
Tendon reflex (any 1 or more)	115	283	67	132	114	262
Arm reflexes	104	280	60	132	101	261
Leg reflexes	51	282	35	129	52	259
Spontaneous movement	36	283	14	132	30	262
Induced movement	46	282	23	128	40	261

*Number of cases in which the clinical examination was performed and with unequivocal ECS at the time of exam.

Table 15

CEPHALIC REFLEXES IN NON-SURVIVORS HAVING COMA, APNEA AND ECS FOR 24 HOURS OR MORE. TIMED FROM ONSET OF 3 CRITERIA

A. Relation to total 24 hour period	
Total No. of Cases	63
All Cephalic Reflexes Absent from 0 hr	56
One or More Cephalic Reflexes Present	7

B. Relation to time	0 hr	6	12	24	Total
No. Cases with one or more Reflexes Present	3	2	5	1	
No. of Reflexes Present, Each Reflex					
Pupillary	0	0	0	0	0
Corneal	1	0	0	1	2
Oculo-ceph.	0	0	0	0	0
Vestib.	0	0	0	1	1
Aud-oc.	0	0	0	0	0
Snout	2	1	3	0	6
Pharyng.	0	0	0	0	0
Swallow	1	0	0	1	2
Cough	0	0	0	0	0
Jaw	1	1	2	1	5

Table 16

SPINAL REFLEXES IN NON-SURVIVORS HAVING COMA, APNEA AND ECS FOR 24 HOURS OR MORE. TIME FROM ONSET OF 3 CRITERIA

A. Relation to Total 24 Hour Period

Total No of Cases	63
All Spinal Reflexes Absent From 0 Hour	8
One or More Spinal Reflexes Present	55

B. Relation to Time		0 hr	6	12	24
No. Cases with One or More Tendon Reflexes Present, Either Unilateral or Bilateral		30	37	32	37
No. of Tendon Reflexes Present					
	1	9	10	8	10
	2	12	13	7	7
	3	3	5	7	8
	4	3	5	4	3
	5	3	4	6	8
No. of Times Present, Each Reflex					
	Biceps	18	26	20	24
	Triceps	21	27	22	27
	Radial	13	15	17	19
	Knee	8	8	13	13
	Ankle	9	15	17	17

Table 17

SPINAL REFLEXES IN CASES HAVING:
(1) COMA, APNEA AND ECS FOR 24 HOURS OR MORE,
(2) NO CEPHALIC REFLEXES DURING THIS TIME, AND
(3) PATHOLOGIC DIAGNOSIS OF BRAIN DEATH (COMPLETE OR INCOMPLETE)

A. Relation to Total 24 Hour Period

Total No. of Cases	18
All Spinal Reflexes Absent from 0 Hour	0
Spinal Reflexes Present One or More Times	18

B. Relation to Time	0 hr	6	12	24
No. Cases with One or More Reflexes Present, Either Unilateral or Bilateral	8	10	11	11
No. of Tendon Reflexes Present				
1	2	4	2	2
2	3	2	2	1
3	1	1	2	4
4	1	2	2	1
5	1	1	3	3
No. Times Present, Each Reflex				
Biceps	4	5	8	7
Triceps	6	6	8	8
Radial	5	5	7	8
Knee	3	4	5	5
Ankle	2	4	7	7

Table 18

MOVEMENTS AND MUSCLE TONE IN NON-SURVIVORS HAVING COMA, APNEA AND ECS FOR 24 HOURS OR MORE.

TIMED FROM ONSET OF 3 CRITERIA

Total No. of Cases	63

Spontaneous Movement

Absent from 0 hour	49
Present at 1 or More Exams	14

Present at Time:

0	6	12	24
2	2	4	7

Induced Movement

Absent from 0 hour	27
Present at 1 or More Exams	36

Present at Time:

0	6	12	24
20	17	19	22

Muscle Tone

Absent from 0 hour	38
Present at 1 or More Exams	25

Present at Time:

0	6	12	24
11	8	9	10

Table 19

MOVEMENTS AND MUSCLE TONE IN CASES HAVING: COMA, APNEA AND ECS FOR 24 HOURS OR MORE, NO CEPHALIC REFLEXES DURING THIS TIME, AND PATHOLOGIC DIAGNOSIS OF BRAIN DEATH (COMPLETE OR INCOMPLETE).

Total No. of cases	18

Spontaneous Movement

Absent from 0 hour	16
Present	2

Time Present:	0	6	12	24
	1			1

Induced Movement

Absent from 0 hour	5
Present	13

Time Present:	0	6	12	24
	5	7	7	8

Muscle Tone

Absent from 0 hour	12
Present	5
Not Examined	1

Time Present:	0	6	12	24
	1	3	2	1

Table 20

HYPOTENSION IN NON-SURVIVORS HAVING COMA, APNEA AND ECS FOR 24 HOURS OR MORE
(63 Cases)

	HOURS			
No. of Recordings of Systolic Pressure Below 80mm	0	6	12	24
	25	25	24	25

Table 21

CORRELATIONS OF CLINICAL TEST RESULTS WITH PATIENT OUTCOMES (BRAIN DEATH VERSUS CARDIAC DEATH OR SURVIVAL)

	Time after First Examination[1]		
Examination	0 hr.	6 hr.	24 hr.
Pupil size	.376***	.266	.396**
Pupillary reflex	.502***	.626***	.640***
Corneal	.293**	.434***	.333**
Oculocephalic	.556***	.457***	.423***
Vestibular	.547***	.566***	.540***
Audio-ocular	-.061	-.057	.293
Snout	.023	.094	.332**
Pharyngeal	.247	.304	.354
Swallow	.199	.481***	.212
Cough	.262	.184	.290
Jaw	.209	.299**	.293
Spinal Biceps	.285	.222	.209
Triceps	.139	.230	.161
Radial	.378	.246	.160
Knee	.314**	.308**	.384**
Ankle	.285	.220	.030
Abdominal	-.029	-.177	-.169
Plantar	.061	.138	.123
Spontaneous	.395***	.280	.464***
Induced	.275	.375***	.352**
Tone	.387***	.337**	.544***
Blood Pressure	.249	.275	.218

** $p < .01$

*** $p < .001$

1. Because of missing data, sample sizes range from 49 to 82.

Table 22

CLINICAL EXAMINATIONS IN DISTINGUISHING BRAIN DEATH CASES FROM NON-BRAIN DEATH CASES. TIMED FROM INITIAL EXAMINATION AFTER ENTRY

Examinations	Time (Hours) 0	6	12	24
Individual:				
Pupillary	.6018	.7750	.6618	.6331
Corneal	.5120	.6305	.5022	.4392**
Oculocephalic	.5580	.5784	.6049	.4392**
Vestibular	.6440	.6804	.6618	.6331
Knee jerk	.5040	.4409	.4813	.5505
Spontaneous Movement	.6018	.5111	.5941	.6389
Induced Movement	.3680**	.4316	.3637**	.3858**
Tone	.5569	.4605	.4034**	.6878
Combination of Two:				
Pupillary-vestibular	.7260	.8666	.8307	.7911
Pupillary-corneal	.7260	.8214	.7436	.7149
Pupillary-oculocephalic	.6856	.8214	.7875	.7149
Corneal-vestibular	.6856	.7754	.7436	.6331
Oculocephalic-vestibular	.6443	.6804	.7436	.6331
Vestibular-Knee jerk	.7310	.6599	.6999	.6306
Vestibular-Spontaneous Movement	.7660	.7708	.8276	.7183
Combination of Three:				
Pupillary-Vestibular-Spontaneous Movement	.8444	.8184	.8718	.7950
Pupillary-Corneal-Vestibular	.7659	.8666	.8307	.7911
Pupillary-Oculocephlic-Vestibular	.7260	.8666	.8734	.7911
Corneal-Vestibular-Spontaneous Movement	.7659	.7708	.8276	.7183
Oculocephlic-Vestibular-Spontaneous Movement	.7659	.7708	.8276	.7183

All values are significant at $p<.001$ except those with asterisks (**) in which $p<.01$.

Table 23

CLINICAL EXAMINATIONS IN DISTINGUISHING BRAIN DEATH CASES FROM NON-BRAIN DEATH CASES. BRAIN DEATH CASES TIMED FROM ONSET OF ECS, AND NON-BRAIN DEATH CASES FROM INITIAL EXAMINATION

Examinations	Time (Hours) 0	6	12	24
Individual:				
Pupillary	.6259	.7734	.7207	.6392
Corneal	.3966	.6187	.4949	.3372
Oculocephalic	.4601	.5611	.6691	.4449
Vestibular	.6259	.6728	.7207	.5536
Knee jerk	.3671	.3473**	.3847	.4105
Spontaneous Movement	.3936	.4404	.4771	.6140
Induced Movement	.2949**	.4078	.3506**	.3878**
Tone	.4474	.3840	.4744	.6746
Combination of Two:				
Pupillary-Vestibular	.7181	.8672	.8183	.7234
Pupillary-Corneal	.6695	.8210	.7703	.6422
Pupillary-Oculocephalic	.6217	.8210	.8183	.7205
Corneal-Vestibular	.6217	.7734	.7207	.5536
Oculocephlic-Vestibular	.5714	.6728	.7703	.5536
Vestibular-Knee jerk	.5590	.5712	.6033	.5619
Vestibular-Spontaneous Movement	.6048	.7285	.7005	.7658
Combination of Three:				
Pupillary-Vestibular-Spontaneous Movement	.6980	.7786	.7521	.7658
Pupillary-Corneal-Vestibular	.6695	.8672	.8183	.7234
Pupillary-Oculocephalic-Vestibular	.6695	.8210	.8650	.7234
Corneal-Vestibular-Spontaneous Movement	.6048	.7285	.7005	.6913
Oculocephalic-Vestibular-Spontaneous Movement	.6048	.7285	.7005	.6913

All values are significant at p<.001 except those with asterisks (**) in which p<.01.

Table 24

SNOUT, AUDIO-OCULAR, AND JAW REFLEXES IN NORMAL SUBJECTS AND HOSPITAL PATIENTS

Normal Subject, Ages 3 to 63 years (n-79).

	Present	Absent
Snout	14	65
Audio-ocular	77	2
Jaw	67	12

Patients, Alert, Various Medical and Surgical Disorders, Ages 19 to 78 (n=30).

	Present	Absent
Snout	12	18
Audio-ocular	26	4
Jaw	8	22

Patients, Drowsy or Post Anesthetic, Ages 42 to 85 (n=16).

	Present	Absent
Snout	6	10
Audio-ocular	13	3
Jaw	7	9

Table 25

Relationship of Primary Diagnosis and Degree of Recovery of the Survivors

	Degree of Recovery			
Primary Diagnosis	Complete	Cerebral Deficit	Ambulation	Total
Drug intoxication	26*	--	1	27
Cardiac disease	2	1	2	5
Cerebral trauma	--	4	--	4
Cerebral vascular disease	1	1	--	2
Metabolic disorder	--	--	1	1
Brain tumor	--	1	--	1
Other	--	3	1	4
TOTAL	29	10	5	44

* 3 of these recovered and were discharged from the hospital but were lost to subsequent followup

Table 26

BLOOD PRESSURE

CEREBRAL ISCHEMIA DUE TO CARDIAC ARREST

	Systolic			Diastolic		
Time After Entry (hours)	ECS	BA	p	ECS	BA	p
0	74.8 ± 36.4*	100.2 ± 15.9	<0.2	26.6 ± 29.8	57.2 ± 34.9	<0.2
6	69.1 ± 36.6	103.6 ± 19.5	<0.1	24.4 ± 29.3	55.6 ± 37.2	<0.2
12	67.8 ± 33.2	111.0 ± 32.1	<0.05	34.1 ± 34.1	52.0 ± 31.1	<0.4
24	85.1 ± 47.6	109.0 ± 29.9	<0.4	47.4 ± 36.4	52.3 ± 39.3	<0.6
48	70.0 ± 47.5	110.8 ± 19.1	<0.2	28.5 ± 33.4	60.0 + 40.6	<0.4

*Mean in mm. Hg. ± standard deviation.

TABLE 27

CLINICAL CRITERIA IN THE IDENTIFICATION OF BRAIN DEATH

CRITERIA	BASIS OF CHOICE			
	Correlation data	Rapid Return in Survivors	Lay Interpretation	High Completion Rate
Recommended				
Coma	(+)	+	+	+
Apnea	(+)	+	+	+
Light Reflex	+	+		+
Vestibular Reflex	+			
Oculocephalic Reflex	+			+
Corneal Reflex	+	+		+
Probable				
Spontaneous Movements	+	+	+	+

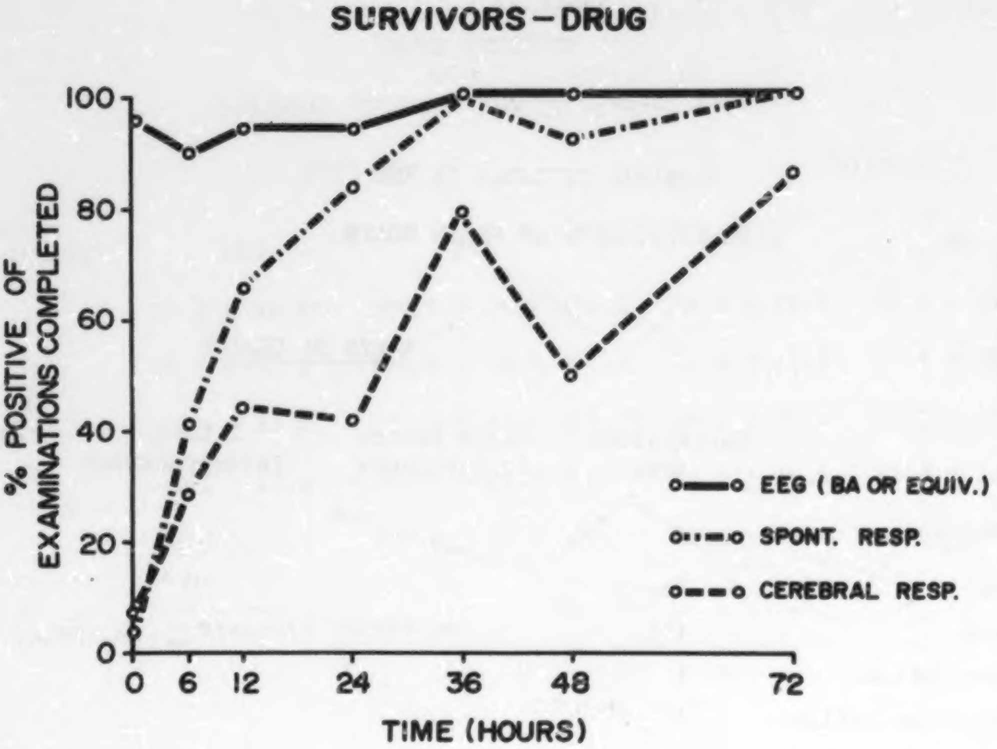

Figure 1. Graph of EEG. Spontaneous respiration and cerebral responsiveness in relation to time after entry into study in drug intoxicated survivors. The small percentage of cases with respirations and cerebral responsivity at 0 hours is accounted for by return of these functions before the first examination could be completed.

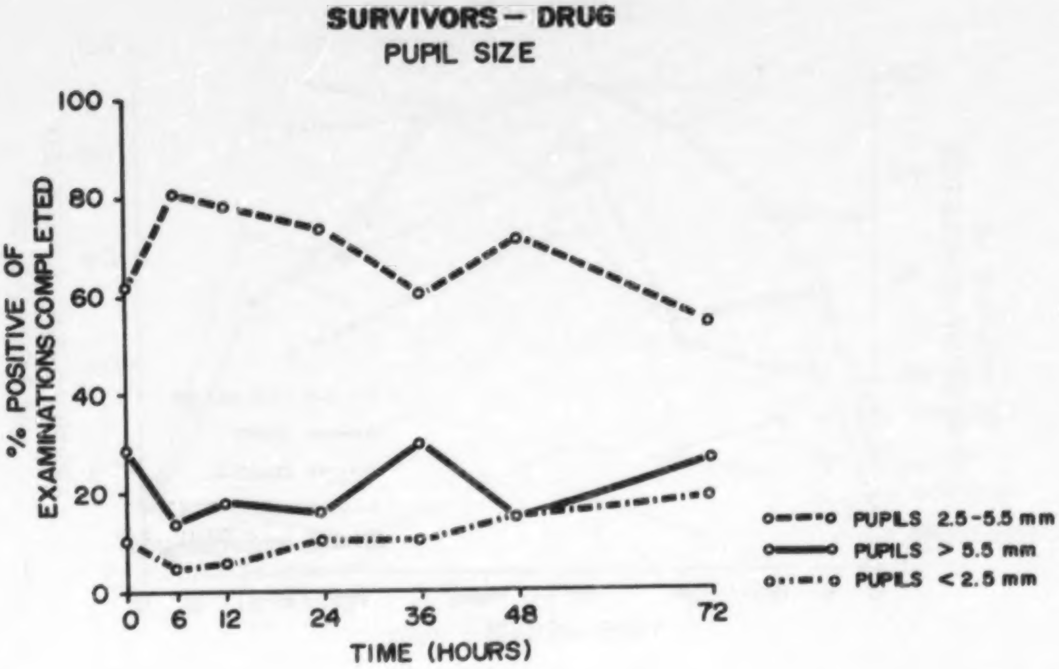

Figure 2. Plot of the pupil size with time in drug survivors showing high percentage of normal sized pupils.

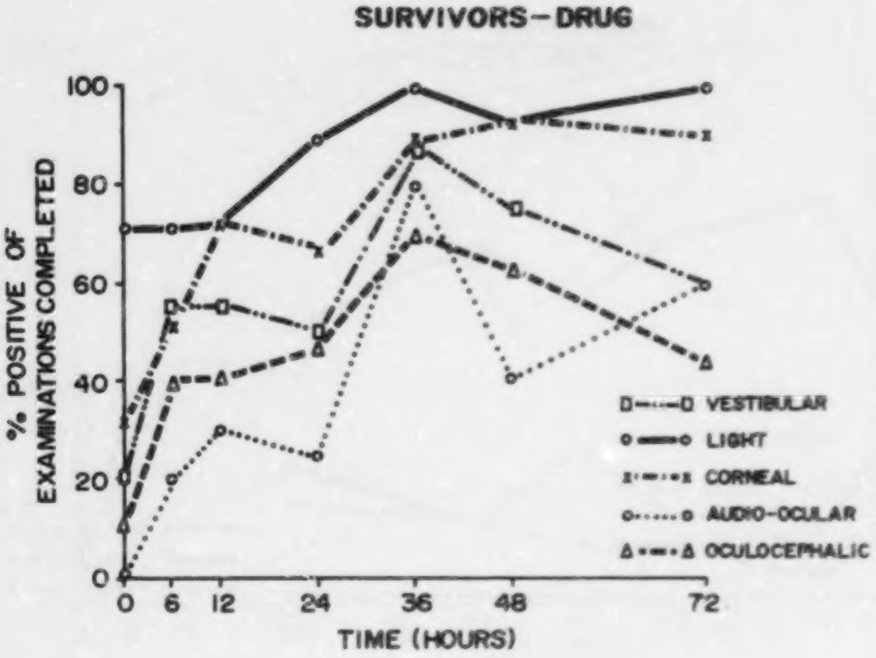

Figure 3. Percent of positive responses for vestibular, pupillary, corneal and ocular reflexes over a 72-hour period after entry into study in drug intoxicated survivors.

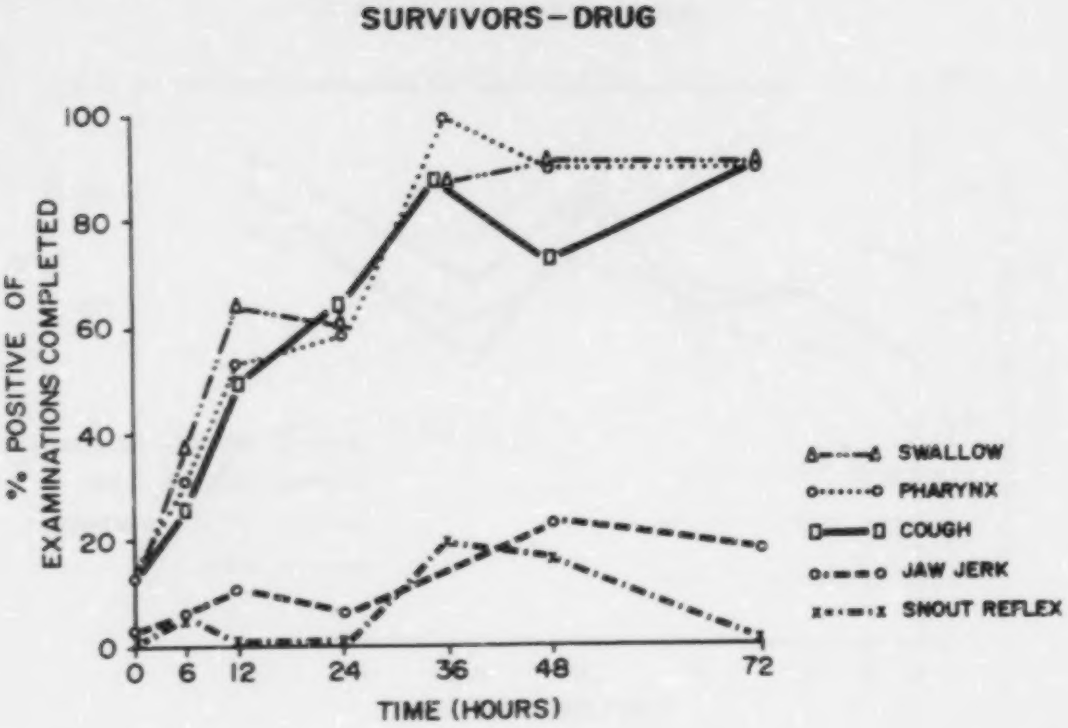

Figure 4. Percent of positive responses for bulbar, jaw and snout reflexes over a 72-hour period after entry into study in drug intoxicated survivors.

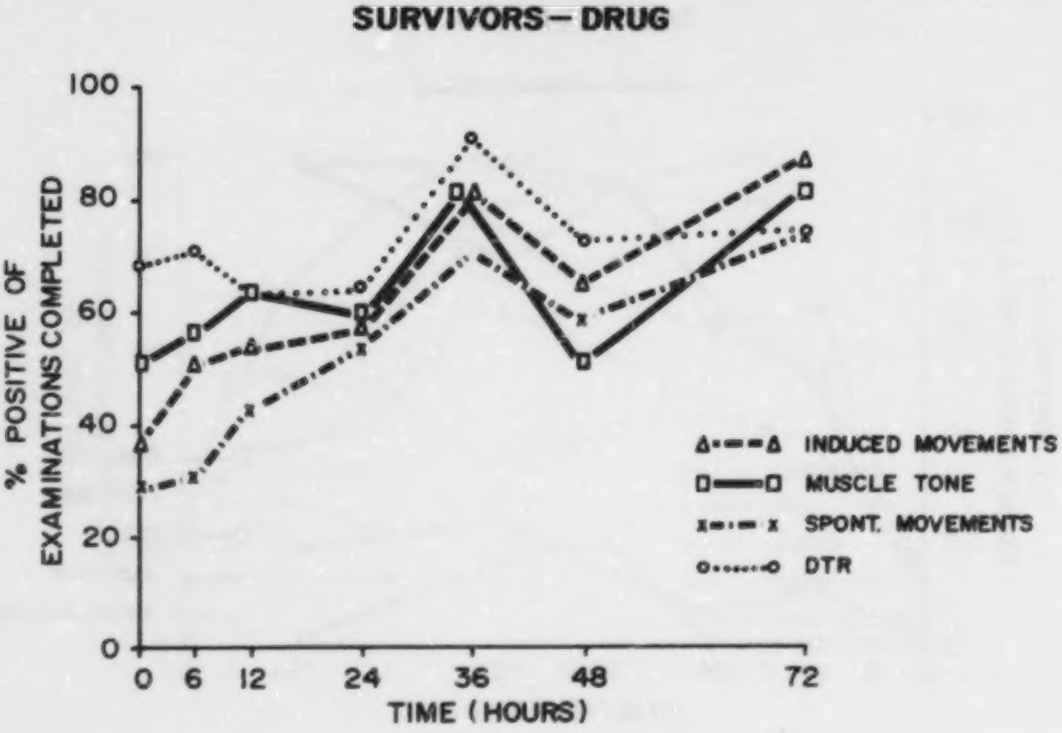

Figure 5. Percent of positive responses for induced movements, muscle tone, spontaneous movements and deep tendon reflexes over a 72-hour period after entry into study in drug intoxicated survivors.

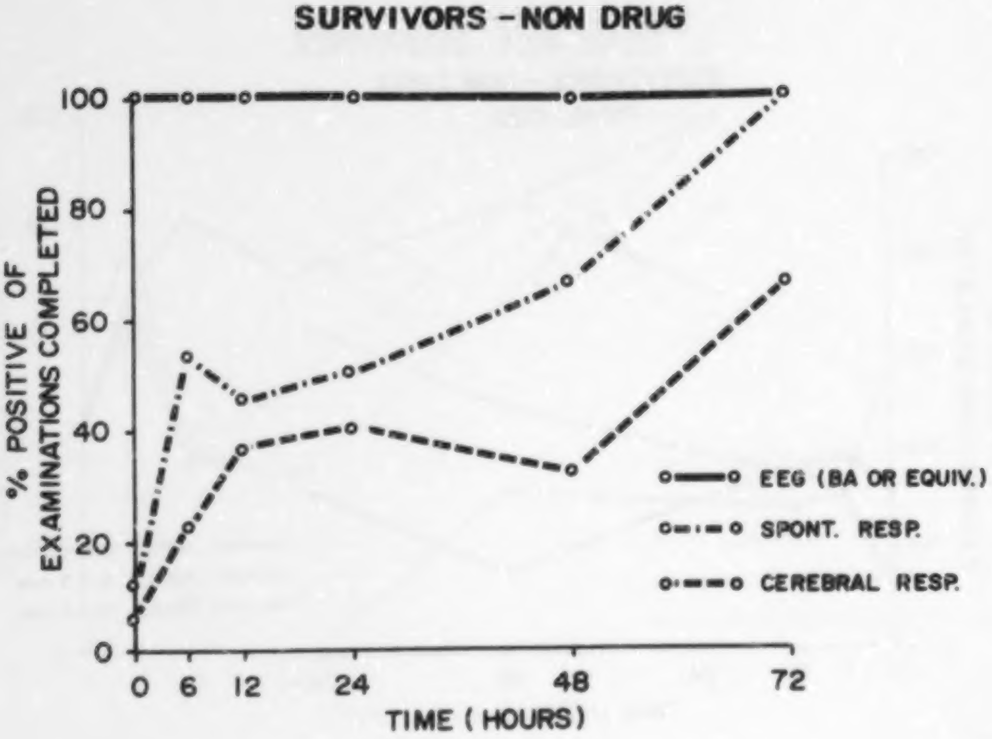

Figure 6. EEG activity and the rate of return of spontaneous respirations and cerebral responsiveness in non-drug intoxicated survivors.

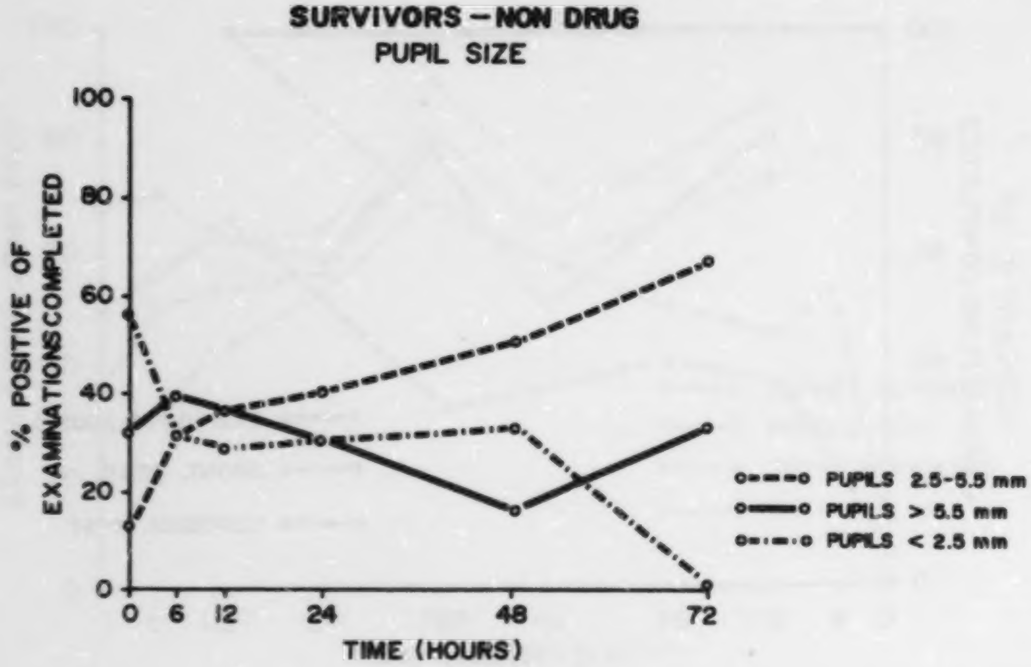

Figure 7. Relationship of pupil size to time in non-drug intoxicated survivors.

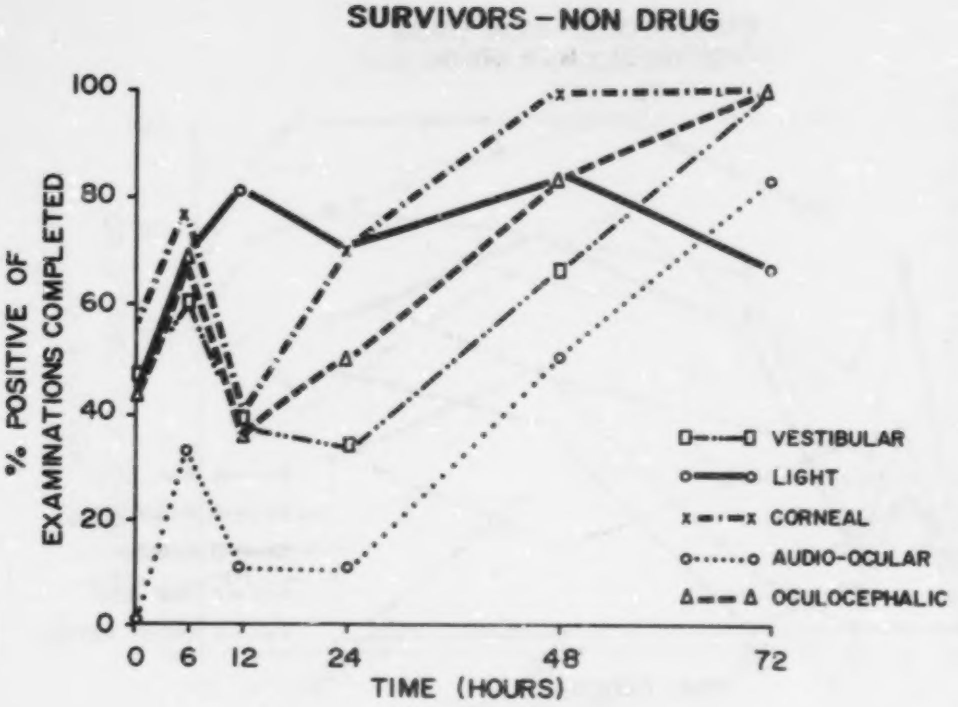

Figure 8. Relationship of positive responses for vestibular, pupillary, corneal and ocular to time in non-drug intoxicated survivors.

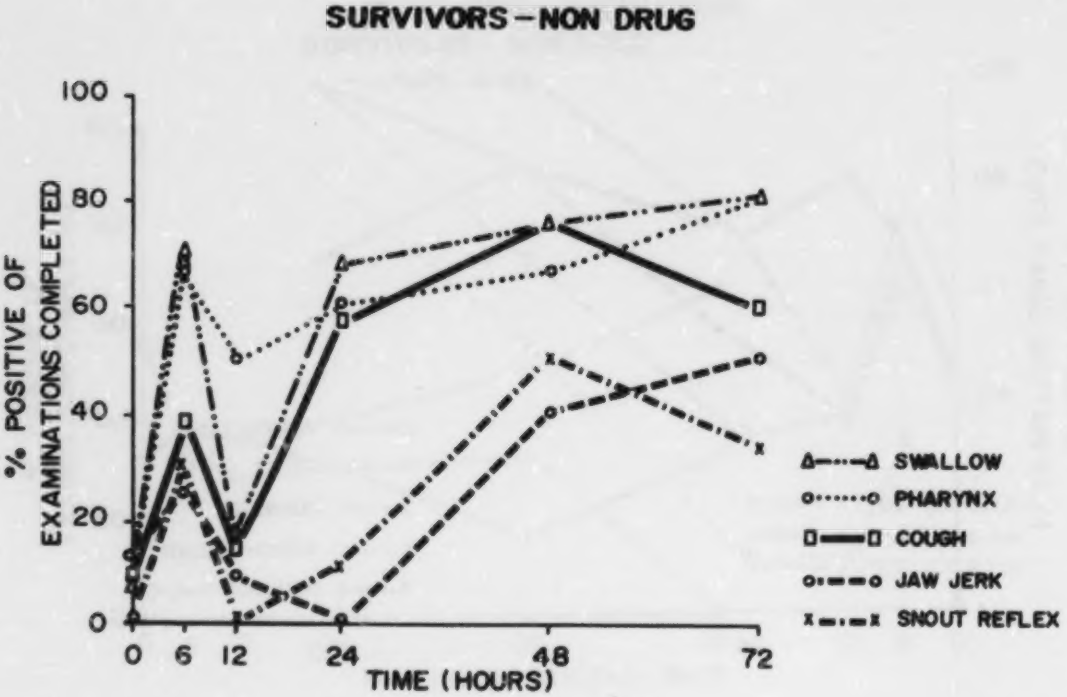

Figure 9. Relationship of positive responses for bulbar, jaw and snout reflexes to time in non-drug intoxicated survivors.

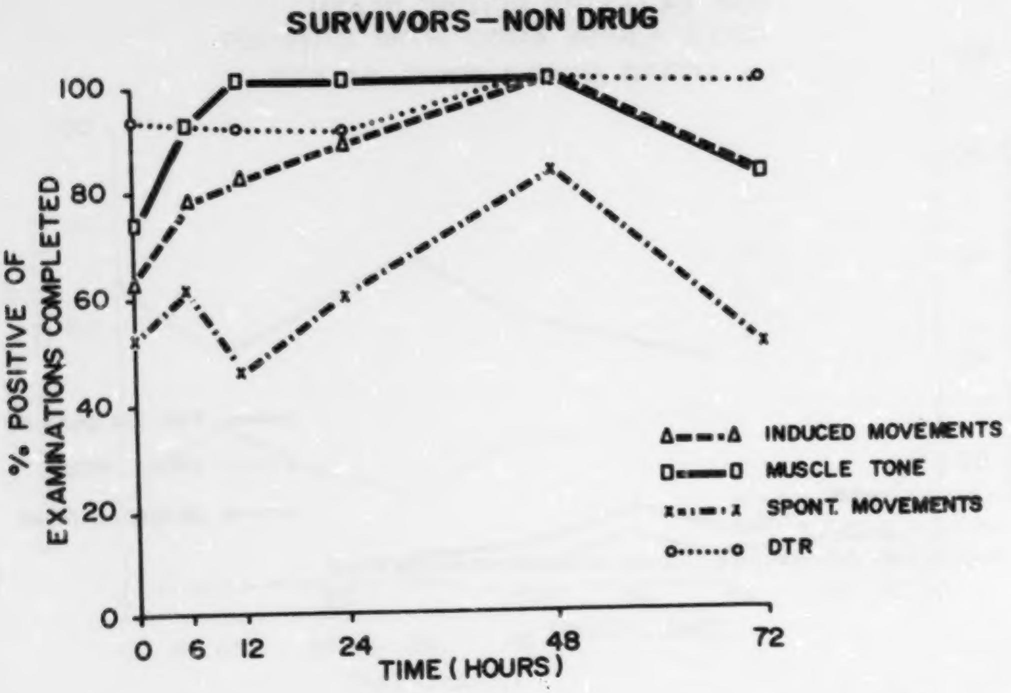

Figure 10. Relationship of positive responses for induced movements, spontaneous movements, muscle tone and deep tendon reflexes to time in non-drug intoxicated survivors.

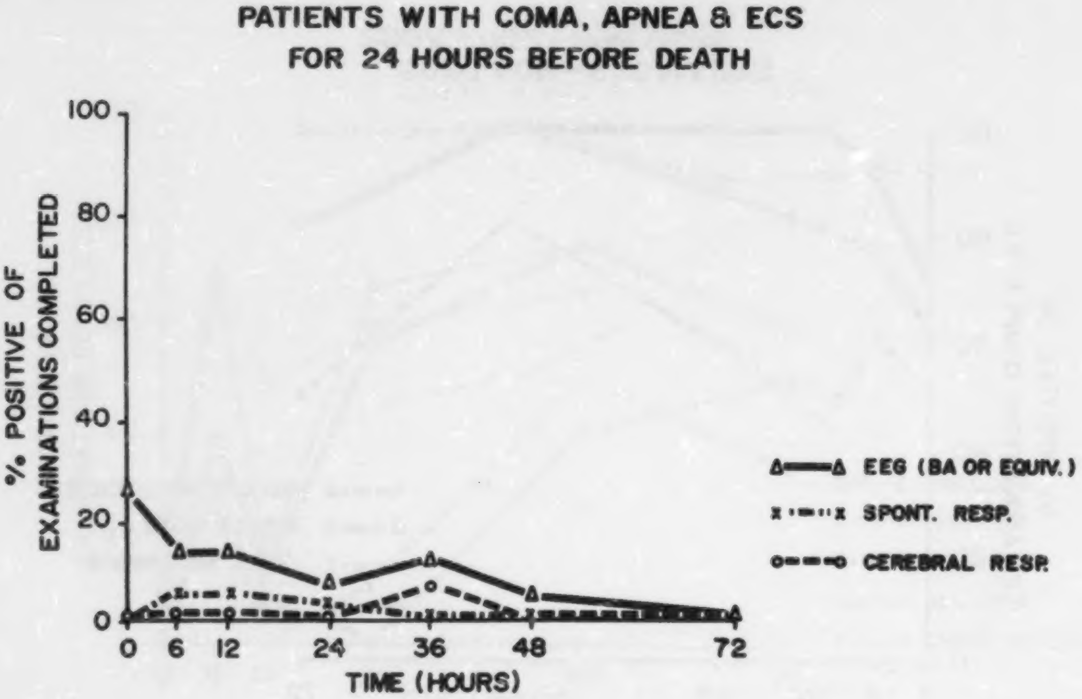

Figure 11. Positive responses for EEG (biological activity or equivocal), spontaneous respirations and cerebral responsiveness after entry into study in patients with presumptive brain death (coma, apnea and ECS for a 24-hour period before cardiac death or cessation or resuscitation).

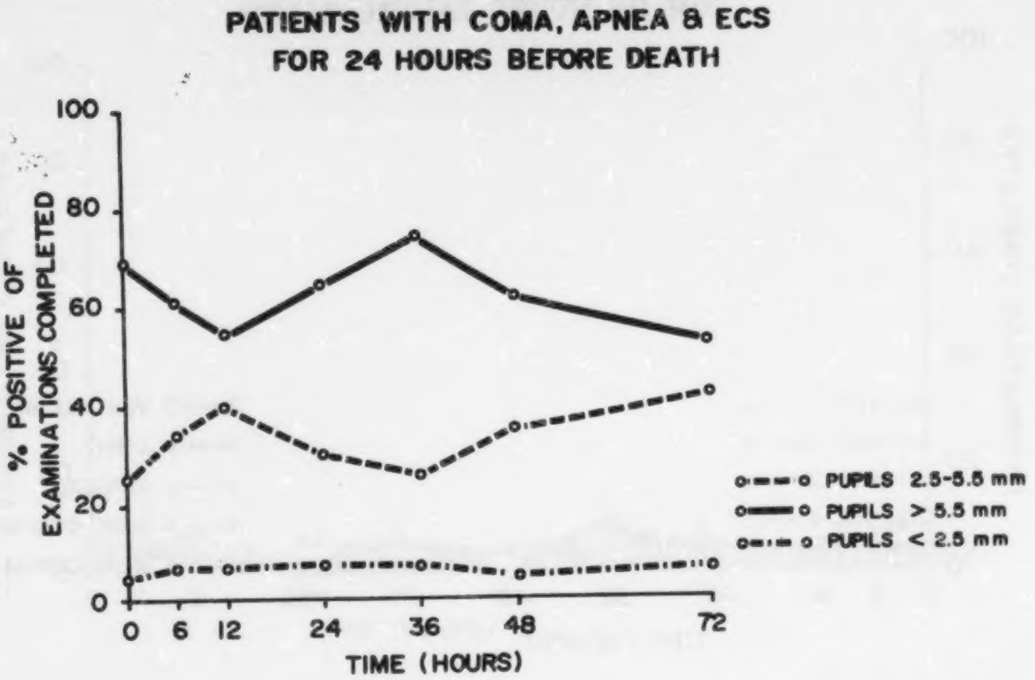

Figure 12. Relationship of pupil size to time in patients with presumptive brain death.

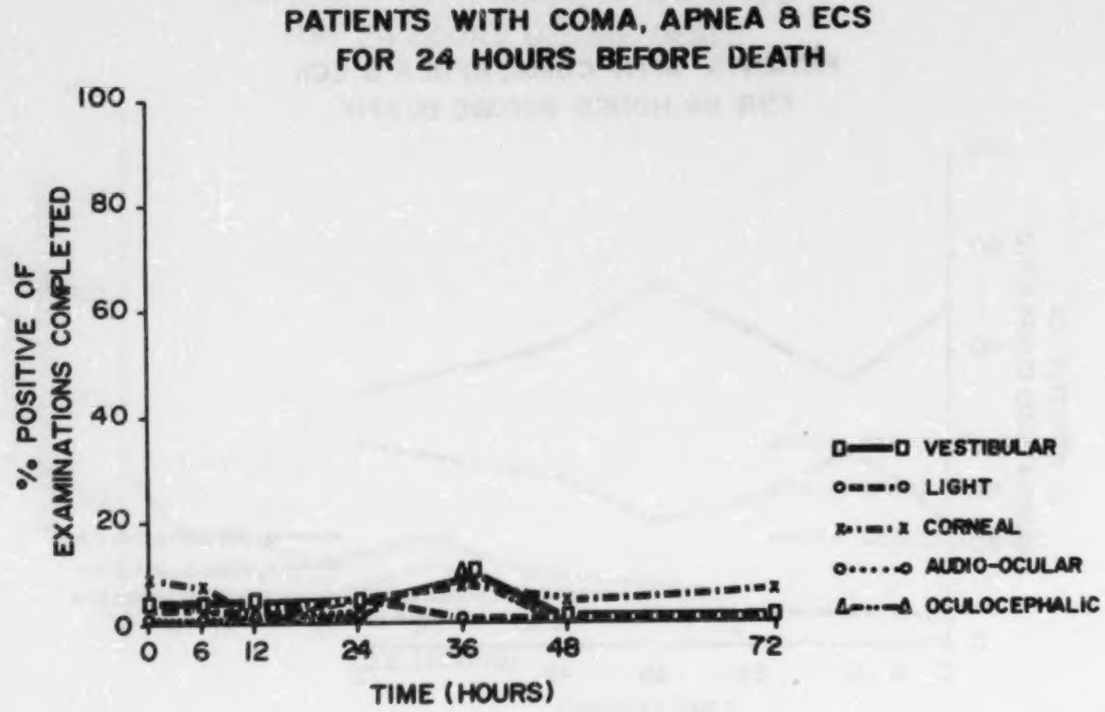

Figure 13. Relationship of positive responses for vestibular, pupillary, corneal and ocular reflexes to time in patients with presumptive brain death.

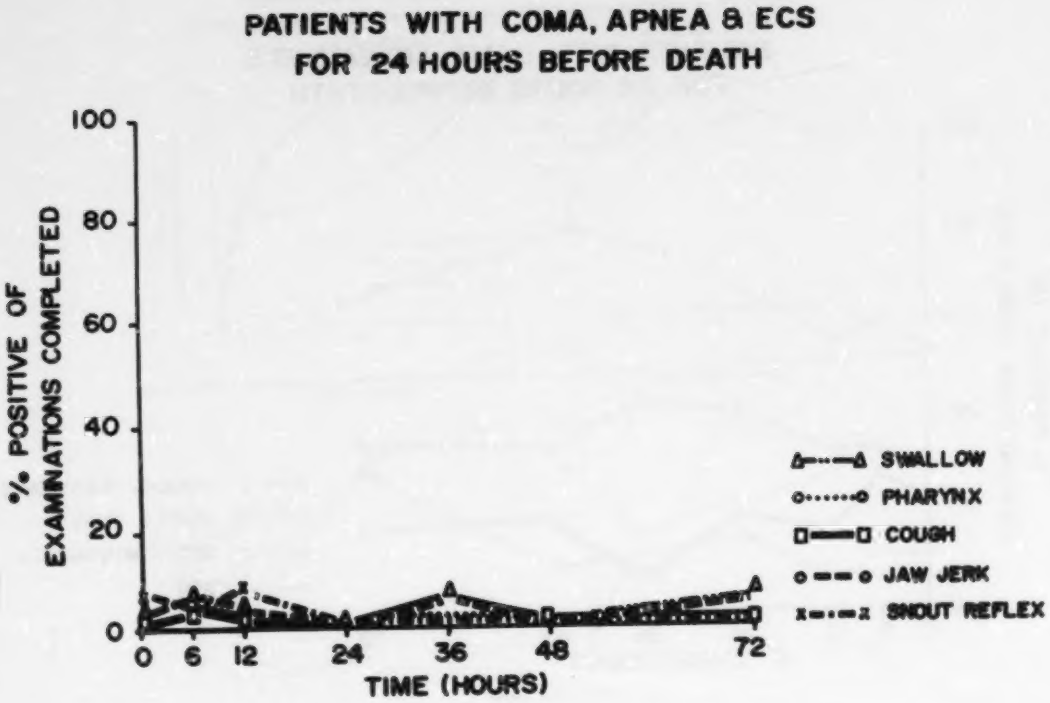

Figure 14. Relationship of positive responses for bulbar, jaw and snout reflexes to time in patients with presumptive brain death.

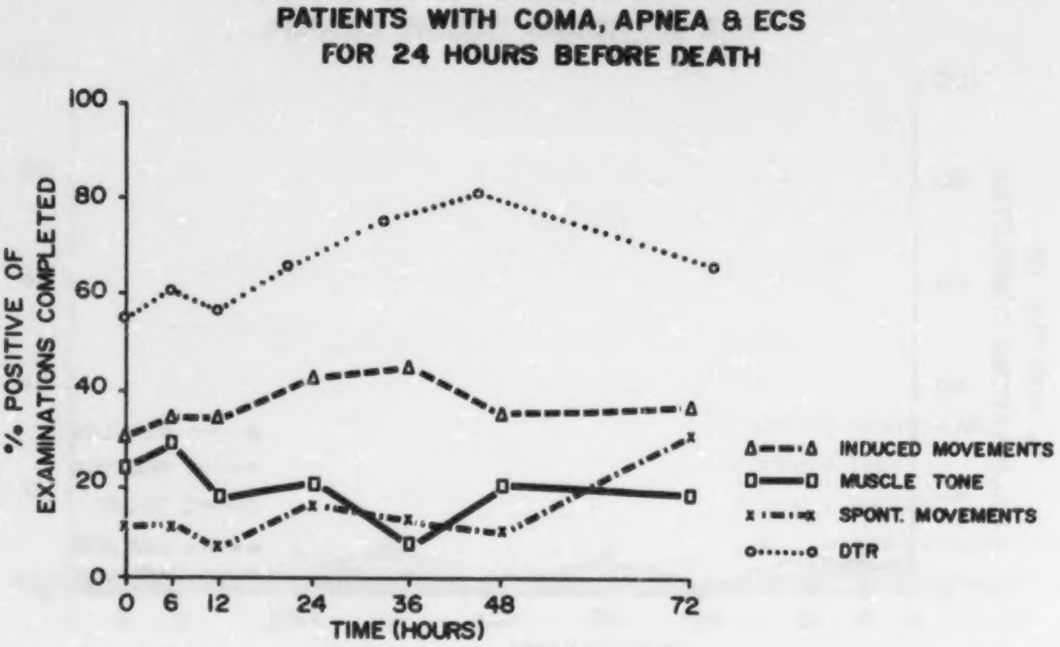

Figure 15. Relationship of positive responses for induced movements, spontaneous movements, muscle tone and deep tendon reflexes to time in patients with presumptive brain death.

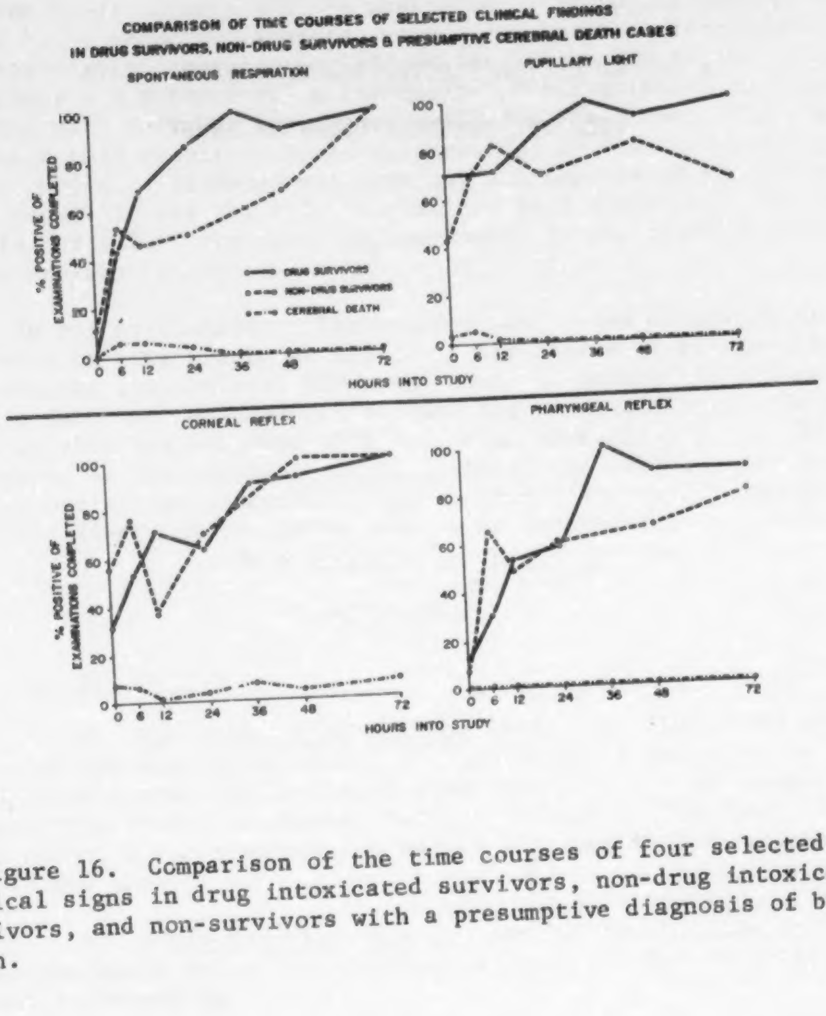

Figure 16. Comparison of the time courses of four selected clinical signs in drug intoxicated survivors, non-drug intoxicated survivors, and non-survivors with a presumptive diagnosis of brain death.

A REVIEW OF THE ELECTROENCEPHALOGRAPHIC DATA FROM THE CEREBRAL SURVIVAL STUDY

by

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INTRODUCTION

The results and conclusions from the cerebral survival study were based on the computation of information from nine geographically separated institutions. In this chapter, the uniformity of the EEG data from these centers will be presented. Categories covered are general data, technical aspects, reader concurrence, interpretations and diagnoses, and the time relationships of the EEG to the clinical evaluations and autopsies. A discussion of the attempts to classify the EEG's with definite brain waves will also be given. The raw data upon which this report is based was provided by the head biostatistician for the project. Although not covering all aspects of the EEG portion of the study, it was the only information made available. The computer analysis for all of the data was programmed by the chief biostatistician and the project coordinator.

In any multicenter collaborative study some discrepancies in the uniformity of data are to be expected; the limits of permissible variation between the centers, however, should be determined before any specific data can be incorporated into the total analysis. To my knowledge this was not done with the data, specifically the EEG experiences in the cerebral survival study; nor were reasons for apparent deviations determined. If a definitive project is planned, acceptable limits of variation have to be determined.

DEFINITIONS

1. EEG Results.

a. Electrocerebral Silence (ECS). An EEG record showing an absence of cerebral potentials over 2 μv during a period of at least 30 minutes from symmetrically placed electrode pairs ≥ 10 cm apart and with interelectrode resistances between 100 and 10,000 ohms. In exceptional cases, a satisfactory EEG may be obtained with a resistance below 25,000 ohms.

b. Brain Activity (B.A.). Any EEG which shows definite spontaneous brain waves irrespective of form, voltage or pattern during a 30-minute recording.

c. Equivocal EEG's (Equiv.). A tracing which the electroencephalographer could not, with any degree of certainty, verify the absence or presence of spontaneous brain waves. This, in many cases, may have been secondary to technical difficulties or artifact.

2. American EEG Standards.--See Minimal Technical Standards for EEG Recording in Suspected Cerebral Death, American EEG Society, Willoughby, Ohio, 1976.

3. Primary Diagnosis.--The primary disease responsible for the unresponsive and apneic state.

4. EEG Segment.--A neurological-EEG combination with the former performed within 6 hours of the tracing (before or after).

5. Initial EEG Segment.--The first EEG-neurological examination after qualification (cerebral unresponsivity and apnea for at least 15 minutes).

6. All EEG Segments.--Total of all EEG-neurological examinations performed within 6 hours of each other.

7. EEG Pattern.--The EEG diagnoses on serial tracings.

0 - No EEG's or all equivocal
2 - All B.A. (some may be equivocal)
4 - All ECS (some may be equivocal)
6 - B.A. then ECS (some may be equivocal)
8 - ECS then B.A. (some may be equivocal)

GENERAL DATA

In table I, the general EEG data is tabulated. The number of cases admitted to the study at each institution showed considerable variation. Center Number 7 withdrew soon after the project began and was replaced by Center Number 9. Forty-two percent of the patients and 43 percent of the records were obtained from two centers (4 and 6). The relative low number of cases admitted from some institutions was never explained. The average number of EEG's per case correlated with the number of ECS records per center (table V). Those centers with the lowest number of EEG's per case had a larger number of patients whose initial EEG showed ECS. Approximately 40 percent of the 156 missed neurological or EEG examinations were from Center Number 4.

Patients under 1 year of age were not entered. Because the number of cases in young children was so small, the EEG-clinical-neuropathological correlations for cerebral death cannot be made for this age group.

TECHNICAL

1. Technically Unacceptable (table IIA).--One hundred and eighteen of the 2,256 (5 percent) records were coded technically unacceptable by the center's electroencephalographer, although this apparently did not preclude the physician from making a final interpretation, i.e. equivocal, brain activity or ECS. Data is not available for the specific reasons; however, one asumes in all likelihood, the major problem was artifact. Fifty percent (60/118) of the technically unsatisfactory EEG's were reported from Center 4. Four of the 29 (14 percent) records called equivocal were technically unacceptable although the number of total EEG's in this category is extremely small. Six and 7 percent respectively of the records classified in EEG patterns 2 and 6 were not acceptable, whereas only 2 percent of the records showing persistent ECS and none of the records with ECS followed by brain activity were classified as unsatisfactory.

2. American EEG Standards (table IIB).--Three percent of the 2,256 EEG's did not meet American EEG standards. Again, specific reasons are not available. Thirty-eight percent (26/68) of these records were from Center 9 whereas from the other centers the range was 0.2 to 6 percent. The percentage of records for each EEG pattern that did not meet American EEG standards was approximately the same, with the lowest value one percent (6/638) from patients who showed ECS in all records.

3. Impedance Above 10,000 Ohms (table IIC).--Seventeen percent of 2,256 (for 3 EEG's the value was not reported) had impedances above 10,000 ohms. It is assumed that the majority of these were recorded at centers where needle electrodes were used. Forty-three percent (161/376) of records with impedances greater than 10,000 ohms were from Center 5. The range was extremely variable, from zero in two centers (3 & 7) to 63 percent at Center 5. It is of interest that only 10 percent of the EEG's from pattern 4 (ECS in all records) were recorded with increased impedances, whereas in patterns 2 and 6--brain activity in all records or brain activity followed by ECS--the percentages were 22 and 16 percent.

4. Muscle Paralyzing Agents (table IID).--In 171/2,256 (8 percent) of the recordings, muscle paralyzing agents were used. No data is available on the particular medication given, although in all likelihood Anectine and pancuronium bromide were administered most frequently. The use of these various agents by center ranged from zero at Center 1 to

31 percent at Center 5. From the other centers the percentage was 7 or below. In only 4 percent of records showing ECS were the agents used. In contrast, they were employed more frequently in the equivocal cases whose EEG's showed activity in all records or activity followed by ECS.

5. Artifact.--Twenty-five percent of all records contained some type of artifact. Muscle accounted for 9.5 percent, EKG 8.2 percent, movement 1.3 percent, and other 5.1 percent. No further breakdown is available for the latter category.

EEG READER CONCURRENCE

Three hundred and three of the 2,256 EEG's from 500 patients were reviewed by a panel of expert electroencephalographers. The records were selected by the project coordinator because he disagreed with the interpretation or found them interesting. Random records were also reviewed. The percentage of the EEG's selected for review from the 9 centers varied considerably, ranging from 2 percent at Center 5 to 49 percent at Center 1 (table III). Also in table III, the results of the panel review are tabulated. There was a difference of opinion on 39 records (13 percent). Twenty-seven percent of the records diagnosed as equivocal, 11 percent as having brain waves and 16 percent of the tracings coded ECS by the center electroencephalographers were reviewed by the panel. There was agreement on 67 percent of the equivocal EEG's, 93 percent of the brain activity tracings and 86 percent of the ECS records. There was complete agreement by the panel with the project electroencephalographer's interpretations with all three EEG diagnoses from Centers 3, 5 and 7. From the remaining centers the difference of opinion for the 3 EEG diagnoses is as follows: Center 1, 2 out of 56; Center 2, 10 out of 30; Center 4, 4 out of 29; Center 6, 10 out of 39; Center 8, 5 out of 49; Center 9, 4 out of 14. Noteworthy are the 9 EEG's interpreted as ECS by the center electroencephalographer but as showing definite brain waves by the panel. Six of these records were from Center 2, 2 from Center 4, and 1 from Center 6.

Of the 7 cases reported to have regained brain waves after showing ECS, only 3 cases are known to have been reviewed by the panel. As shown in table IV, there was a difference in interpretation in all 3 cases by the review panel. Noteworthy is Case Number 5 who showed recovery of brain activity after 2 records showing ECS. The patient was in coma secondary to hepatic insufficiency.

INTERPRETATIONS

Six percent of the 482 initial EEG's (1st examination-EEG) were read as equivocal, 36 percent ECS and 58 percent as showing definite brain waves (table V-A). A similar ratio was noted for all EEG examinations (table V-B). For the various EEG patterns the percent showing either ECS or brain waves in all records was approximately the same (40 percent) (table V-C). Three percent of all records remained equivocal. Eighty-four of the 482 (17 percent) patients showed initial brain activity and then subsequent ECS. Only five patients had initial ECS and then on subsequent EEG's either definite brain waves or equivocal activity. In one patient a neurological examination was not done within 6 hours of the EEG.

As would be expected, the percentages for the three EEG diagnoses as well as patterns varied among the centers (tables V A-C). Several differences were noted.

1. Six of the 9 institutions reported equivocal records with a range between 3-10 percent for the initial recording and 0.3-9 percent for all tracings. Noteworthy was the absence of equivocal reports from 3 centers. In addition, only 1 of 255 records from Center 5 was read as equivocal.

2. From 5 centers the number of initial records with brain waves was higher than for ECS (range 60-82 percent), from one institution (Center 2) approximately the same and at three centers ECS records predominated (range 58-64 percent). For all EEG's this ratio remained approximately the same; however, from Centers 7 and 9 the total number of records showing brain activity approximately equalled those interpreted as ECS although the number of patients entered into the study from these two institutions was limited. Three hundred and twenty-six of the 843 ECS records (39 percent) were recorded from Center 6.

3. The number of patients with ECS in all records or initial brain activity followed by ECS was again higher from Centers 1, 6 and 7 (85, 79 and 70 percent) and lowest from Centers 5 and 8 (34 and 32 percent). From the other centers the range was between 47 and 58 percent. This variance of data may indicate clinical or procedural differences in the cases studied at the various centers. To evaluate this, the EEG interpretations were correlated with the primary diagnoses and the elapsed time for qualification until the initial EEG segment.

PRIMARY DIAGNOSIS

The primary diagnoses responsible for the unresponsive state and respiratory arrest are listed by center in table VI. Since the number of patients for each specific disease by center is limited, they have been arbitrarily divided into primary intracranial, secondary intracranial and other diseases (not specified) so that a comparison of the EEG diagnoses between the various centers could be made. Because the number of patients from Centers 7 and 9 was small, the data from these institutions is not included in the subsequent analysis. From Centers 1, 2, 3, 4, 6, and 8, the number of patients with a primary intracranial diagnosis was greater than those with an extracranial cause, particularly from Center 6 (74 percent of that center's patients). From Center 5 the number of patients with an extracranial cause was slightly higher. For the third category, i.e. other diagnoses, the percentage of the total cases/center ranged between 6 and 17 percent, with the highest from Centers 2 and 3.

In table VII the percentages of the initial and all ECS segments based on the combined total of the ECS and brain activity segments by center is tabulated. (Equivocal tracings and records from other disease categories were excluded.) From only two centers (1 and 6) did ECS tracings exceed those with brain waves for both categories (initial and subsequent EEG's). For primary intracranial diseases, ECS records (initial and total) were approximately 10 percent higher than records with brain activity from Center 2. From the other institutions, records with brain waves were approximately 10 percent higher than ECS tracings for this particular category.

The biggest discrepancy between the percent of ECS to brain wave recordings on the initial segments was in the secondary intracranial category where the ratio was approximately 1:3-6 for four centers. From Center 5, no initial ECS records were reported in 19 patients. From Centers 1 and 6, however, ECS tracings were approximately 10 percent higher than those with brain waves. Differences in the percentages between the initial and all EEG segments for both categories are most likely related to the number of patients whose initial EEG showed activity and then ECS or patients with initial ECS who died soon after admission. The results from Center 1 for secondary intracranial diseases which showed a marked increase in the number of ECS records on followup examinations is an example.

As previously mentioned, the number of patients as well as the total number of records for a specific disease by center is limited. However, from a few centers with a reasonable number of cases and records for cerebral ischemia, a difference was noted (table VIII). Sixty-two and 49 percent of the initial and subsequent EEG segments from Center 6 showed ECS. For Centers 3, 4 and 8, these percentages were significantly lower. The percentage of ECS with head trauma and subarachnoid plus intracranial hemorrhage was similar between Centers 4 and 6 for all segments (table VIII).

The data indicates a variance between essentially two centers (1 and 6) and the other institutions for the percent of ECS tracings on the initial as well as subsequent recordings. The difference was most marked for secondary intracranial diagnoses. The reasons for this are not apparent. Although specific time intervals from hours eligible to the first EEG segment are not available for primary and secondary intracranial diseases, a delay in the examination does not appear to be a factor (table IX). For example, 73 percent of the examinations from Center 5 with a low percentage of ECS records took place within 11.9 hours of qualification while from Center 6 with a high percentage of ECS tracings 71 percent were performed within the same time frame. For the combined data from all centers, however, EEG's performed soon after qualification showed a higher percentage of B.A. records (table X).

Hours Eligible to First Exam-EEG.--In table IX the cumulative percentages for the lapse time between qualification and the first EEG segment are listed. For Centers 4, 5, 6, 7, 8, and 9, over 50 percent (range 39-85 percent) of the initial examinations were done within 6 hours and approximately 70 percent within 12 hours of qualification. However, for Centers 1, 2 and 3, this latter percentage was not reached until approximately 24 hours after qualification. The EEG data from all patients irrespective of whether the first segment was done 12, 24, 36 hours, etc. after qualification was included in the final report to NIH.

Timing of the Neurological Examination and EEG.--In table XI the times the neurological examinations were performed in relationship to the EEG are tabulated. Twenty percent of the EEG's were performed prior to and 80 percent after the examination. Between 54-57 percent of the neurological examinations were done within 0.9 hour at 4 centers (5, 6, 8 and 9) while less than 39 percent (range 22-38) were accomplished within this time frame at the other institutions. Within 2 hours, over 70 percent of the clinical evaluations were performed at all centers. The final report correlating the EEG diagnosis with the neurological findings included the data from all examinations performed within 6 hours of the EEG.

Classification of EEG's With Brain Waves.--Prior to and during the study, several attempts to develop a classification code for the EEG's showing definite brain waves were made. Several protocols were submitted based primarily either on frequency and amplitude analysis or pattern recognition. When subject to initial preliminary evaluation, the degree of interreader concurrence was such that they were not further pursued. Despite this several of the centers submitted a supplementary grant to NIH for further study of this important issue. They felt that a classification code could be developed with reasonable interreader concurrence. This grant was not funded. A limited pilot computer project was also conducted by the University of California in San Diego to determine if any specific EEG abnormalities (frequency, amplitude, or pattern) could be used as predictors of eventual ECS. Because of technical problems, this project was also terminated.

It is indeed unfortunate that a classification system was not developed and adequately tested before this study was started. Because of this, 1,311 records with brain activity, one of the largest collections of serial EEG's in deeply comatose patients with clinical and neuropathological correlations that has ever been collected, has been lost for critical analysis.

An important practical example would have been the documentation of the longest interval of absent cerebral activity between bursts (burst supression pattern) when recorded at a sensitivity of 2 mv/mm and increased interelectrode distances. If this could have been determined, then the total duration of a recording required to establish definite ECS could have been determined. In the author's personal experience, the longest period of supression was approximately 25 seconds in a patient with drug-induced coma. It may have been determined that only several minutes are required for the determination of ECS rather than the recommended 30 minutes.

Since the early 1950's, the value of various electroencephalographic abnormalities in coma (ECS excluded for the most part) correlated with clinical neuropathological and prognostic data has been a controversial subject. This study could have provided possible answers to some of the debatable issues thus preventing unnecessary duplication of effort and expenditures of monies. Perhaps, more importantly, it could have provided new insights into the pathophysiology of coma as well as uncovered different approaches and techniques for the study of this problem.

Mortality and Autopsy Rate.--In table XII the EEG pattern and the final end are listed. Of the 44 patients who survived or were lost to followup, all but two had brain waves in their first and subsequent EEG's (pattern 2). The two patients with initial ECS followed by brain activity (pattern 8) were comatose from drug overdose. The major diagnoses of the 44 patients who survived were as follows: 27 - drug intoxication, 5 - ischemia secondary to cardiac and/or respiratory arrest, 4 - cerebral trauma, 4 - other diseases not specified, and 1 each for subarachnoid hemorrhage, other vascular disease, metabolic disorders and neoplasms. The percent survival was highest from Center 8, accounting for 36 percent of the total survivors (16 out of 44). The primary diagnosis in 13 of these patients was exogenous intoxication.

Resuscitation was discontinued in 114 of the 459 deaths (table XII). The EEG's from 110 of these patients were classified in patterns 4 and 6. Thus, the number of cases for the study of duration of "life" after the first ECS recording is limited (37 patients from pattern 4 and 25 from pattern 6). Data was not available for comparing the differences between "cardiac death" and "resuscitation discontinued" for the nine centers.

The autopsy percentages by EEG pattern by center are listed in table XIII; these ranged between 21 and 88 percent. From five centers the autopsy rate was greater than 50 percent. There was little difference in the total autopsy rate for the EEG patterns although some individual variations were noted between centers. Autopsy rates for patterns 4 and 6 were higher than for pattern 2 from Centers 1, 2, 5, and 7. Fifty-two of the 110 autopsied cases with ECS in all records came from Centers 1 and 6. There did not appear to be an appreciable difference in the number of autopsies for the various primary diagnoses.

The pathological CNS changes should be correlated not only with the primary diagnoses, but also to the elapsed time from qualification to death, i.e. duration on respirator (respirator brain). Statistics were not available for the time interval from qualification to the first EEG to death for the autopsied cases. However, in table XIV, the EEG pattern of the autopsied cases who died within 12 hours of the last examination by center is tabulated (patterns 0 and 8 omitted). The number of cases after this time interval is also shown. Seventy-one percent of the autopsied patients died within 12 hours of the last EEG examinations. Again, variations between the EEG patterns and autopsy rates at some institutions are noted. For pattern 2, the percentage was 50 percent. It would be expected, however, that the number of autopsied cases (death within 12 hours of last EEG) for this pattern would be less than for patterns 4 and 6 since these patients survived longer. Consequently, the time interval between the examinations was longer. The neuropathological-EEG correlations reported to NIH as well as published elsewhere were based on all autopsied cases irrespective of the time interval from the last EEG. Consequently, the pathology data from 66 patients where death occurred 12 hours after the last EEG-examination were included in these reports.

SUMMARY AND CONCLUSIONS

In table XV a center comparison for major procedural and technical standards is shown. The standards, although for the most part arbitrarily selected, were also based on an appreciation of the difficulties in performing this pilot collaborative study, i.e. initial notification and then coordination of serial EEG and neurological examinations on critically ill patients, most of these cared for in intensive care units. As the chart illustrates, there was considerable variation between the centers for the 14 major categories. Not one center satisfied all 14 criteria, nor did all centers meet the standards for a particular category. Centers 2 and 4 met only 5 and 4 of the 14 standards, respectively. An appreciation of these variations is not only important for understanding the limitations of the EEG correlations (clinical and neuropathological) in the final report to NIH but also need to be considered if a definitive project is planned, i.e. to establish permissible limits based on the experiences from the pilot study before particular EEG data can be used for analysis. Examples would be a decision whether to include the results of a neurological examination whose associated EEG was called technically unacceptable by the center electroencephalographer, or did not meet the American EEG standards. Should the records on which there was a difference in interpretation between the project electroencephalographer and the reviewer be included? What is an acceptable time interval between the EEG and neurological examination or the last EEG and death (autopsied cases) for meaningful correlations? Careful on-line monitoring of the data from all centers is also essential in order to detect procedural or technical differences early in the study, so that corrective action can be taken. This was not done in the pilot study.

An analysis of the ratio of ECS records to those with brain activity, on the initial as well as all tracings, suggests a difference in the clinical state of the patients at some centers. Part of this may be accounted for by the primary diagnosis, i.e. intracranial or extracranial and the time lapse between qualifications and the first EEG. However, one would have to question whether this may have been secondary to variations in techniques for determining the presence of apnea at the various centers, i.e. the centers with the highest percent of patients with ECS were more precise in determining the absence of spontaneous respirations than the other institutions. In a definitive study, the tests for determining apnea need to be better defined.

Finally, if a definitive study is planned, a classification code for EEG's with brain activity should be developed and pretested before the study begins.

TABLE I

GENERAL EEG DATA

CENTER	1	2	3	4	5	6	7	8	9	Total
# Pts	36	46	74	121	38	91	14	67	16	503
% of Total	7%	9%	15%	24%	8%	18%	3%	13%	3%	
# EEGs	114	158	344	421	255	538	52	306	68	2256
Ave Number/Case	3.2	3.4	4.6	3.5	6.7	5.9	3.7	4.6	4.3	4.49
% of Total Records	5%	7%	15%	19%	11%	24%	2%	14%	3%	
Neuro Exam-No Associated EEG	5/90(6%)	11/90(12%)	3/90(3%)	37/90(41%)	7/90(8%)	13/90(14%)	4/90(4%)	9/90(10%)	1/90(1%)	90
EEG-No Associated Neuro Exam	4/66(6%)	8/66(12%)	8/66(12%)	23/66(35%)	2/66(3%)	14/66(21%)	2/66(3%)	3/66(5%)	2/66(3%)	66
TOTAL	9/156(6%)	19/156(12%)	11/156(7%)	60/156(39%)	9/156(6%)	27/156(17%)	6/156(4%)	12/156*8%)	3/156(2%)	156

TABLE IIA

TECHNICAL ASPECTS OF EEGs

PERCENT RECORDS TECHNICALLY UNACCEPTABLE X CENTER X EEG PATTERN X ALL EEGs

CENTER EEG Pattern	1	2	3	4	5	6	7	8	9	Total	% of Total Records Technically Unacceptable
0	0/0	0/4	0/6	4/7	0/0	0/2	0/0	0/10	0/0	4/29(14%)	4/2256(0.2%)
2	0/20	4/51	9/203	31/185	0/182	1/137	4/23	12/223 (8)	7/24	68/1048(6%)	68(2256(3%)
4	0/62	1/65	2/43	6/112	0/23	1/252	0/25	0/38 (0)	0/18	10/638(2%)	10/2256(0.4%)
6	0/32	1/26	7/92	19/106	0/50	7/128	0/4	2/35 (1)	0/26	36/499(7%)	36/2256(2%)
8	0/0	0/12	0/0	0/11	0/0	0/19	0/0	0/0 (0)	0/0	0/42(0%)	0/42(0%)
Total	0/114(0%)	6/158(4%)	18/344(5%)	60/421(14%)	0/255(0%)	9/538(2%)	4/52(8%)	14/306(5%)	7/68(10%)	118/2256(5%)	118/2256(5%)

TABLE IIB

TECHNICAL ASPECTS OF EEGs

PERCENT AMERICAN EEG STANDARDS NOT MET X CENTER X EEG PATTERN X ALL EEGs

CENTER EEG Pattern	1	2	3	4	5	6	7	8	9	Total	% of Total Records EEG Standards Not Met
0	0/0	0/4	0/6	1/7	0/0	0/2	0/0	0/10	0/0	1/29(3%)	1/2256 (.04%)
2	0/20	1/51	1/203	6/185	2/182	1/137	3/23	6/223	20/24	40/1048(4%)	40/2256 (2%)
4	1/62	0/65	0/42	5/112	0/23	0/252	0/23	0/38	0/18	6/638(1%)	6/2256 (0.3%)
6	0/32	0/26	5/92	2/106	0/50	0/128	0/4	0/35	6/26	13/499 (3%)	12/2256 (0.6%)
8	0/0	0/12	0/0	1/11	0/0	0/19	0/0	0/0	0/0	1/42 (2%)	1/2256 (.04%)
Total	1/114(1%)	1/150(1%)	6/344(2%)	15/421(4%)	2/255(1%)	1/538(.2%)	3/52(6%)	6/306(2%)	26/68(38%)	61/2256(3%)	61/2256(3%)

TABLE IIC

TECHNICAL ASPECTS OF EEGs

PERCENT IMPEDANCE ABOVE 10,000 OHMS X CENTER X EEG PATTERN X ALL EEGs

CENTER EEG Pattern	1	2	3	4	5	6	7	8	9	Total	% of Total Records with Impedance ↑ 10,000 ohms
0	0/0	0/4	0/6	0/7	0/0	1/2	0/0	0/10	0/0	1/29 (3%)	1/2256 (.04%)
2	2/20	11/50	0/201	4/185	110/182	24/137	0/23	60/223	18/24	229/1045 (22%)	229/2256(10%)
4	0/62	13/65	0/43	2/112	19/23	22/252	0/25	8/38	0/18	64/638 (10%)	64/2256 (3%)
6	0/32	6/26	0/92	1/106	32/50	35/128	0/4	0/35	6/26	80/499 (16%)	80/2256 (4%)
8	0/0	2/12	0/0	0/11	0/0	0/19	0/0	0/0	0/0	2/42 (5%)	2/42 (.09%)
Total	2/114(2%)	32/157*(20%)	0/342*(0%)	7/421(2%)	161/255(63%)	82/538(15%)	0/52(0%)	68/306(22%)	24/68(35%)	376/2253(17%)	376/2253 (17%

* 3 records impedances not reported
(1 Center 2 and 2 Center 3)

TABLE IID

TECHNICAL ASPECTS OF EEGs

PERCENT MUSCLE RELAXANTS USED X CENTER X EEG PATTERN X ALL EEGs

CENTER	1	2	3	4	5	6	7	8	9	Total	% of Total Records Muscle Relaxants Used
EEG Pattern											
0	0/0	0/4	0/6	0/7	0/0	0/2	0/0	4/10	0/0	4/29 (14%)	4/2256 (0.2%)
2	0/20	7/51	9/203	3/185	67/182	4/137	5/23	13/223	2/24	110/1048 (11%)	110/2256 (5%)
4	0/62	4/65	0/43	0/112	0/23	18/252	2/25	2/38	0/18	26/638 (4%)	26/2256 (1%)
6	0/32	0/26	4/92	0/106	13/50	8/128	2/4	2/35	0/26	29/499 (6%)	29/2256 (1%)
8	0/0	0/12	0/0	0/11	0/0	2/19	0/0	0/0	0/0	2/42 (5%)	2/2256 (.09%)
Total	0/114 (0%)	11/158 (7%)	13/344 (4%)	3/421 (1%)	80/255 (31%)	32/538 (6%)	9/52 (17%)	21/306 (7%)	2/68 (3%)	171/2256 (8%)	171/2256 (8%)

TABLE III

READER CONCURRENCE

RECORDS REVIEWED BY CENTER

CENTER	1	2	3	4	5	6	7	8	9	Total
# Records Reviewed / Total # of Records	56/114 (49%)	30/158 (19%)	48/344 (14%)	29/421 (7%)	6/255 (2%)	49/538 (9%)	22/52 (42%)	49/306 (16%)	14/68 (21%)	303/2256 (13%)
# Equivocal Records	0	11	20	36	1	13	0	21	0	102
# Equivocal Records Reviewed	0 (0%)	7 (64%)	4 (20%)	6 (17%)	1 (100%)	3 (23%)	0 (0%)	6 (29%)	0 (0%)	27 (27%)
Panel Agrees	0	4	4	1	1	3	0	5	0	18 (67%)
Panel ECS	0	0	0	0	0	0	0	1	0	1
Panel Equivocal	0	0	0	0	0	0	0	0	0	0
Panel Active	0	3	0	5	0	0	0	0	0	8
# Not Reviewed	0	4	16	30	0	10	0	15	0	75

TABLE III (Continued)

READER CONCURRENCE

CENTER	1	2	3	4	5	6	7	8	9	Total
# Brain Wave Records	38	74	250	235	222	199	26	231	36	1311
# Brain Wave Records Reviewed	18 (47%)	10 (14%)	39 (16%)	16 (7%)	0 (0%)	15 (8%)	9 (35%)	31 (13%)	5 (14%)	143 (11%)
Panel Agrees	17	9	39	15	0	10	9	27	5	131 (92%)
Panel ECS	1	1	0	1	0	4	0	4	0	11
Panel Equivocal	0	0	0	0	0	1	0	0	0	1
Panel Active	0	0	0	0	0	0	0	0	0	0
# Not Reviewed	20	64	211	219	0	184	17	200	31	946

CENTER	1	2	3	4	5	6	7	8	9	Total
# ECS Records	76	73	74	150	32	326	26	54	32	843
# ECS Records Reviewed	38 (50%)	13 (18%)	5 (7%)	7 (5%)	5 (16%)	31 (10%)	13 (50%)	12 (22%)	9 (28%)	133 (16%)
Panel Agrees	37	7	5	5	5	26	13	12	5	115 (86%)
Panel ECS	0	0	0	0	0	0	0	0	0	0
Panel Equivocal	1	0	0	0	0	4	0	0	4	9
Panel Active	0	6	0	2	0	1	0	0	0	9
# Not Reviewed	38	60	69	143	27	295	13	42	23	710

TABLE IV

ECS to B.A.

Case	Diagnosis	Time entry until EEG Center Interpretation Review Panel	Survival
#1	Drug Intoxication	12 hrs 24 hrs ECS → B.A. Review - not known	yes (CR)*
#2	Drug Intoxication	0 hrs 6 hrs 20 hrs 46 hrs ECS → ECS → ECS → B.A. Review - not known	yes (CR)
#3	Subarachnoid Hem.	1 hr 6 hrs 11 hrs 25 hrs ECS → ECS → ECS → B.A. Review - not known	No
#4	Reyes Syndrome	5 hrs 11 hrs 18 hrs ECS → B.A. → ECS B.A. B.A. B.A.	No
#5	Hepatic Coma	1 hr 6 hrs 11 hrs ? ? ECS → ECS → Equiv → Equiv → Equiv ECS ECS B.A. B.A. B.A.	No
#6	Drug Intoxication	2 hrs 24 hrs 38 hrs 51 hrs 73 hrs ECS → B.A. → B.A. → B.A. → B.A. Review - not known	No
#7	Hydrocephalus, Cerebellar Anomalies & Spinal Cord Glioma	? ? ? ? ? B.A. → B.A. → ECS → B.A. → ECS x 4 B.A. → B.A. → B.A. → B.A. → ECS x 4	No

*CR - complete recovery

TABLE V-A

INTERPRETATION X INITIAL EEG (First Exam-EEG) X CENTER

CENTER	1	2	3	4	5	6	7	8	9	Total
EEG DIAGNOSIS										
Equivocal	0 (0%)	3 (7%)	3 (4%)	11 (10%)	1 (3%)	5 (6%)	0 (0%)	6 (9%)	0 (0%)	29 (6%)
Brain Activity	12 (36%)	20 (49%)	53 (73%)	66 (60%)	31 (82%)	33 (37%)	5 (39%)	47 (70%)	11 (69%)	278 (58%)
ECS	21 (64%)	18 (44%)	17 (23%)	34 (31%)	6 (16%)	52 (58%)	8 (62%)	14 (21%)	5 (31%)	175 (36%)
Total	33	41	73	111	38	90	13	67	16	482
No EEG	3	5	1	10	0	1	1	0	0	21

TABLE V-B

INTERPRETATION X ALL EEGs X CENTER

CENTER	1	2	3	4	5	6	7	8	9	Total
EEG DIAGNOSIS										
Equivocal	0 (0%)	11 (7%)	20 (6%)	36 (9%)	1 (0.3%)	13 (2%)	0 (0%)	21 (7%)	0 (0%)	102 (4%)
Brain Activity	38 (33%)	74 (47%)	250(73%)	235(56%)	222(87%)	199(37%)	26 (50%)	231(75%)	36 (53%)	1311 (56%)
ECS	76 (67%)	73 (46%)	74 (22%)	150(36%)	32(13%)	326(61%)	26 (50%)	54(18%)	32 (47%)	843 (36%)
Total	114	158	344	421	255	538	52	306	68	2256
No EEG	5	11	3	37	7	13	4	9	1	90

TABLE V-C

EEG PATTERN X NUMBER OF PATIENTS (Exam & EEG) X CENTER

CENTER	1	2	3	4	5	6	7	8	9	Total
EEG PATTERN										
0	0 (0%)	1(2%)	2 (3%)	4 (4%)	0 (0%)	2 (2%)	0 (0%)	4 (6%)	0 (0%)	13 (3%)
2	5 (15%)	15 (37%)	37 (51%)	45 (41%)	25 (66%)	15 (17%)	4 (31%)	41 (61%)	7 (44%)	194 (40%)
4	21 (64%)	19 (46%)	18 (25%)	38 (34%)	7 (18%)	55 (61%)	8 (62%)	15 (22%)	5 (31%)	186 (39%)
6	7 (21%)	5 (12%)	16 (22%)	22 (20%)	6 (16%)	16 (18%)	1 (8%)	7 (10%)	4 (25%)	84 (17%)
8	0 (0%)	1 (2%)	0 (0%)	2 (2%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	5 (1%)
Total	33	41	73	111	38	90	13	67	16	482
No EEG	3	5	1	10	0	1	1	0	0	21

TABLE VI

PRIMARY DIAGNOSIS X NUMBER OF PTs X CENTER
(Divided into primary and secondary intracranial causes and others not specified)

CENTER	1	2	3	4	5	6	7	8	9	Total
DIAGNOSIS										
PRIMARY INTRACRANIAL										
1. Trauma	5	9	13	23	4	27	2	11	0	94
2. Thrombosis	2	0	1	4	6	5	2	4	1	25
3. SA hemorrhage	2	5	6	4	3	5	3	4	2	34
4. Embolism	1	1	1	2	0	0	0	2	1	8
5. Intracerebral Hemorrhage	4	5	8	25	2	18	1	8	3	74
6. Vascular Disease - Other	0	1	0	3	0	2	1	2	0	9
7. Infection	3	1	3	2	1	6	0	1	0	17
8. Neoplasm	2	1	1	1	0	4	0	2	1	12
	19	23	33	64	16	67	9	34	8	273
SECONDARY INTRACRANIAL										
1. Ischemia (Cardio and/or resp. arrest)	9	5	19	29	7	14	4	14	4	105
2. Metabolic	5	7	5	4	11	2	0	1	1	36
3. Exogenous Intoxication	1	3	5	12	1	0	0	13	1	36
	15	15	29	45	19	16	4	28	6	177
Other Diseases (not specified)	2	8	12	12	3	8	1	5	2	53
TOTAL	36	46	74	121	38	91	14	67	16	503

TABLE VII

% ECS/TOTAL RECORDS (B.A. & ECS) X INITIAL EEG SEGMENT AND ALL SEGMENTS X DIAGNOSIS X CENTER

CENTER	1		2		3		4		5		6		8	
Segment	Initial/All													
Primary Intracranial	10/17	37/67	13/21	51/84	12/30	44/111	24/52	111/185	6/15	27/103	42/64	262/370	12/29	45/121
	59%	55%	62%	61%	40%	40%	46%	60%	40%	26%	66%	71%	41%	37%
Secondary Intracranial	9/14	33/41	3/12	11/49	2/29	14/151	7/39	22/156	0/19	5/142	9/15	49/97	2/28	9/143
	64%	81%	25%	23%	7%	9%	18%	14%	0%	4%	60%	51%	7%	6%
Total	19/31	70/108	16/33	62/133	14/58	58/262	31/91	133/341	6/34	32/245	51/79	311/467	14/57	54/264
	61%	65%	48%	47%	24%	22%	34%	39%	18%	13%	65%	67%	25%	21%

TABLE VIII

PRIMARY DIAGNOSIS X EEG DIAGNOSIS X INITIAL SEGMENT X ALL SEGMENTS X CENTER
(B.A. or ECS)

		Initial Segment				All Segments			
	CENTER	3	4	6	8	3	4	6	8
DIAGNOSIS									
Ischemia	B.A.	17 (94%)	20 (87%)	5 (39%)	12 (86%)	91 (95%)	83 (88%)	46 (51%)	58 (87%)
	ECS	1 (6%)	3 (13%)	8 (62%)	2 (14%)	5 (5%)	11 (12%)	45 (49%)	9 (13%)
	TOTAL	18	23	13	14	96	94	91	67
	CENTER		4	6			4	6	
Trauma	B.A.		8 (50%)	8 (32%)			22 (33%)	37 (26%)	
	ECS		8 (50%)	17 (68%)			45 (67%)	108 (74%)	
	TOTAL		16	25			67	145	
	CENTER		4	6			4	6	
Subarachnoid Hemorrhage & Intracerebral Hemorrhage	B.A.		12 (48%)	9 (41%)			20 (27%)	44 (30%)	
	ECS		13 (52%)	13 (59%)			54 (73%)	101 (70%)	
	TOTAL		25	22			74	145	

TABLE IX

CENTER X HOURS ELLIGIBLE X FIRST EXAM-EEG

CUMULATIVE PERCENTAGES

CENTER	1	2	3	4	5	6	7	8	9	Total
Time (hrs)										
0-5.9	13/32 41%	12/40 30%	25/72 35%	61/110 55%	21/37 57%	44/90 49%	11/13 85%	51/67 76%	10/16 63%	248/477 52%
0-11.9	16/32 50%	18/40 45%	32/72 44%	76/110 69%	27/37 73%	64/90 71%	11/13 85%	61/67 91%	14/16 88%	319/477 57%
0-17.9	16/32 58%	23/40 58%	41/72 57%	92/110 84%	32/37 86%	74/90 82%	12/13 92%	66/67 94%	16/16 100%	372/477 78%
0-23.9	21/32 66%	28/40 70%	49/72 68%	97/100 88%	33/37 89%	78/90 87%	12/13 92%	67/67 100%	16/16 100%	401/477 84%
0-35.9	27/32 84%	29/40 73%	53/72 74%	103/110 94%	36/37 97%	83/90 92%	13/13 100%	67/67 100%	16/16 100%	427/477 90%
0-47.9	30/32 94%	33/40 83%	55/72 76%	107/110 97%	36/37 97%	86/90 96%	13/13 100%	67/67 100%	16/16 100%	443/477 93%
0-71.9	31/32 97%	35/40 88%	58/72 81%	109/110 99%	37/37 100%	88/90 98%	13/13 100%	67/67 100%	16/16 100%	454/477 95%
0-72+	32/32 100%	40/40 100%	72/72 100%	110/110 100%	37/37 100%	90/90 100%	13/13 100%	67/67 100%	16/16 100%	477/477 100%
TOTAL # of patients	32	40	72	110	37	90	13	67	16	477
Unknown or No EEG*	4/36 11%	6/46 13%	2/74 3%	11/121 9%	1/38 3%	1/91 1%	1/14 7%	0/67 0%	0/16 0%	26/503 5%

*-3 Initial EEGs missed

TABLE X

EEG PATTERN (B.A. OR ECS) X HRS ELIGIBLE X FIRST EXAM-EEG X EEG PATTERNS 2, 4 & 6

		Time (Hrs)	0-5	6-11	12-23	24-35	36-47	48-71	72+	Total	Unknown or No EEG
A	ECS	# & % ECS	86/240	31/68	33/79	9/24	8/16	7/11	10/22	184/460	13
		Total # Records for Time Interval	36%	46%	42%	37%	50%	64%	45%	40%	
B	B.A.	# & % B.A.	154/240	37/68	46/79	15/24	8/16	4/11	12/22	276/460	7
		Total # Records for Time Interval	64%	54%	58%	63%	50%	36%	55%	60%	

TABLE XI

EEG X TIME NEUROLOGICAL X ALL SEGMENTS X CENTER

CENTER	1	2	3	4	5	6	7	8	9	Total
Time (Hrs) 0-0.9	40/110 36%	48/150 32%	110/336 33%	151/398 38%	143/253 57%	284/524 54%	11/50 22%	167/303 55%	37/66 56%	991/2190 45%
1-1.9	42/110 38%	69/150 46%	156/336 46%	131/398 33%	80/253 32%	197/524 38%	28/50 56%	116/303 38%	19/66 29%	838/2190 39%
2-2.9	13/110 12%	27/150 19%	50/336 15%	71/398 18%	23/253 9%	41/524 8%	9/50 18%	15/303 5%	10/66 15%	259/2190 12%
3-4.9	15/110 14%	6/150 4%	16/336 5%	42/398 11%	7/253 3%	2/524 0.4%	2/50 4%	3/303 1%	0/66 0%	93/2190 4%
5-5.9	0/110 0%	0/150 0%	4/336 1%	3/398 1%	0/253 0%	0/524 0%	0/50 0%	2/303 1%	0/66 0%	9/2190 0.4%
TOTAL Exam & EEG	110	150	336	398	253	524	50	303	66	2190
Exam - No Associated EEG	5	11	3	37	7	13	4	9	1	90/156 58%
EEG - No Associated Exam	4	8	8	23	2	14	2	3	2	66/156 42%
Total	119	169	347	458	262	551	56	315	69	156

447 EEGs Before - 20%
1743 EEGs After - 80%

TABLE XII

EEG PATTERN X FINAL END

EEG PATTERN	CARDIAC DEATH	RESUSCITATION STOPPED	IMPROVED NO DEFICIT	IMPROVED WITH DEFICIT	IMPROVED TO AMBULATION	LOST TO FOLLOW UP
0	15	1	0	0	0	0
2	155	1	24	10	5	3
4	117	80	0	0	0	0
6	55	30	0	0	0	0
8	3	2	2	0	0	0
Total	345	114	26	10	5	3

TABLE XIII
EEG PATTERN X DEATH X AUTOPSY X CENTER

CENTER # Autopsy / # Died EEG PATTERN	1	2	3	4	5	6	7	8	9	Total
0	0/0	1/1	0/2	3/7	0/0	1/2	0/0	1/4	0/0	6/16 (38%)
2	3/4 (75%)	6/13 (46%)	10/33 (30%)	18/37 (49%)	14/23 (61%)	7/11 (64%)	2/5 (40%)	16/25 (64%)	0/5 (0%)	76/156 (49%)
4	21/23 (91%)	18/22 (82%)	3/18 (17%)	18/43 (42%)	5/7 (71%)	31/56 (55%)	5/8 (63%)	8/15 (53%)	1/5 (20%)	110/197 (56%)
6	6/7 (86%)	3/5 (66%)	7/17 (41%)	9/22 (41%)	4/6 (67%)	7/16 (44%)	1/1 (100%)	6/7 (86%)	2/4 (50%)	45/85 (53%)
8	0/0	1/2	0/0	1/1	0/0	1/2	0/0	0/0	0/0	3/5 (52%)
Total	30/34 (88%)	29/43 (67%)	20/70 (29%)	49/110 (45%)	23/36 (64%)	47/87 (54%)	8/14 (57%)	31/51 (61%)	3/14 (21%)	240/459 (52%)

TABLE XIV

EEG PATTERN X EEG WITHIN 12 HOURS OF DEATH X AUTOPSIED CASES X CENTER

CENTER EEG PATTERN	1	2	3	4	5	6	7	8	9	Total
2	1/3	4/6	4/10	8/18	9/14	3/7	1/2	8/16	0/0	38/76
	(33%)	(67%)	(40%)	(44%)	(64%)	(43%)	(50%)	(50%)	(0%)	(50%)
4	20/21	15/18	3/3	11/18	5/5	21/31	3/5	8/8	0/1	86/110
	(95%)	(83%)	(100%)	(61%)	(100%)	(68%)	(60%)	(100%)	(0%)	(78%)
6	6/6	3/3	6/7	8/9	4/4	5/7	1/1	6/6	2/2	41/45
	(100%)	(100%)	(86%)	(89%)	(100%)	(71%)	(100%)	(100%)	(100%)	(91%)
Total	27/30	22/27	13/20	27/45	18/23	29/45	5/8	22/30	2/3	165/231
	(90%)	(82%)	(65%)	(60%)	(78%)	(64%)	(63%)	(73%)	(67%)	(71%)

EEG PATTERN X EEG PATTERN AFTER MORE THAN 12 HRS X AUTOPSIED CASES

EEG PATTERN	2	4	6	Total
TIME				
12-23 hours	15	19	1	35
24+ hours	17	3	3	23
Unknown	6	2	0	8
Total	38	24	4	66

TABLE XV

A SUMMARY OF PROCEDURAL AND TECHNICAL DIFFERENCES BETWEEN CENTERS

CATEGORY	CENTER 1	2	3	4	5	6	7	8	9	Total
# Pts > 50	-	-	+	+	-	+	-	+	-	4
Neuro Exam - No Associated EEG and vice versa < 10%	+	-	+	-	+	-	+	+	+	6
Technically Unacceptable EEGs < 10%	+	+	+	-	+	+	+	+	+	8
American EEG Standards not met < 10%	+	+	+	+	+	+	+	+	-	8
Impedance > 10,000 ohms < 10%	+	-	+	+	-	-	+	-	-	4
Records reviewed by panel > 20%	+	-	-	-	-	-	+	+	+	4
% Reader Concurrence > 90% all EEGs	+	-	+	-	+	-	+	+	-	5
1st EEG Segment Without 5.9 hrs. of Eligibility > 50%	-	-	-	+	+	+	+	+	+	6
1st EEG Segment Without 11.9 hrs. of Eligibility >75%	-	-	-	-	-	-	+	+	+	3
1st EEG Segment Without 23.9 hrs. of Eligibility > 100%	-	-	-	-	-	-	-	+	+	2

TABLE XV

A SUMMARY OF PROCEDURAL AND TECHNICAL DIFFERENCES BETWEEN CENTERS (Continued)

	CENTER									
CATEGORY	1	2	3	4	5	6	7	8	9	Total
Neuro & EEG Segment Within 1 hr. All Segments $>$ 50%	–	-	-	-	+	+	-	+	+	4
Neuro & EEG Within 2 hrs. All Segments $>$ 75%	+	+	+	-	+	+	+	+	+	8
Autopsy Rate $\geq$ 50%	+	+	-	-	+	+	+	+	-	6
Autopsied Pts. with EEG Within 12 hrs. of Death $\geq$ 75%	+	+	-	-	+	-	-	-	-	3
TOTAL	9	5	7	4	9	7	10	12	8	71

CRITERIA OF CEREBRAL DEATH
A Critique

by

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INTRODUCTION

As the result of technical advances in resuscitation, the systemic circulation may now be maintained after some organs, particularly the brain, have suffered irreparable damage. Thus, a dead brain becomes interred in a living body--a paradoxical situation with many medical, ethical, and theological implications. To resolve some of the medical problems, the National Institute of Neurological Diseases and Stroke (U.S.A.) established a collaborative study, in which nine centers participated.

The detailed results of this study are presented elsewhere (1), so that only a brief summary of the program and findings will be given here. At each center, every patient admitted in coma and unable to breathe for 15 minutes was entered in the study. The treatment of the patient remained the responsibility of the attending physician. The investigating team independently examined the patient documenting 1) the clinical state, 2) the neurological condition, and 3) the electroencephalographic findings, initially and every 6 hours for the first 12 hours, then at 24 hours and thereafter once a day until death or recovery.

The primary conditions responsible for the coma and apnea were cardiac diseases (20 percent), head injuries (18 percent), cerebrovascular diseases including hemorrhage, thrombosis, and aneurysm (28 percent), exogenous intoxication (78 percent), and a miscellaneous group comprised of metabolic disturbances, brain tumors, etc. Autopsies were obtained in 240 of the 503 cases admitted to the study.

On the basis of this series, some sets of criteria of cerebral death proposed by organizations, committees or individuals will be examined for prediction of cardiac asystole, electrocerebral silence (ECS), and respirator brain (RB). These criteria are based upon the clinical status, the electroencephalographic (EEG) findings, and the cerebral blood flow (CBF). Before discussing these standards, however, some general consideration should be given to the state of cerebral death.

Like many other terms for specific conditions, cerebral death is a concept without precise clinical or pathological bases. As such, certain arbitrary attributes are commonly sought to indicate its presence. However, how many or how much of these factors must be present to satisfy its occurrence is rarely stated. Is it the absence of the neural organization which constitutes biological life as contrasted to social existence, or is it the absence of any neuronal response, even though the presence of that activity does not serve a functional goal? For example, does the existence of an evoked potential negate the presence of a dead brain? Clinical practice does not consider these precise physiological reactions--in fact, it entirely ignores them by neglecting to examine specifically for their presence. Hence, one must consider cerebral death, as conceived by the practicing physician, as a state of relative neurological inactivity. Consequently, the criteria of cerebral death are relative and predict only with a certain degree of accuracy those individuals in a population of brain death suspects who will meet the common standards for death. Obviously both the degree of accuracy and the proportion of the population accepted will depend upon the number and restrictiveness of the criteria. Hence, to assess the criteria in common use, one can set up arbitrary standards--such as ECS, respirator brain or cardiac asystole--and compare the number of a population achieving these goals using different sets of criteria. If by one set of criteria 100 percent of the candidates will have ECS, RB, and die, whereas by another only 50 percent achieve these goals, the assumption would seem logical, that for these standards, the second criteria are too restrictive.

Before examining the various sets of criteria, it would seem appropriate to define some of the commonly used terms--apnea, coma, death, electrocerebral silence (ECS), respirator brain, and survival.

Apnea is defined as the clinical necessity for a respirator during a period of, at least, 15 minutes. In the early phases of the study, a 3-minute period off the respirator was tried as a check for spontaneous respiration, but when it was found that even 4 1/2 minutes off the respirator was insufficient time for the pO_2 to fall to levels sufficiently low to stimulate respiration, the potential danger of damage to other organs was considered to overweigh the possible value of this test. When resuscitative procedures were stopped on the basis of other manifestations of cerebral death, respiratory efforts were seen in approximately 2 percent of the cases, but rarely did they persist for more than a minute and never were they sufficient to maintain respiratory function.

Coma (cerebral unresponsivity) is a state in which the patient does not respond purposively to externally applied stimuli, obeys no commands, and does not phonate spontaneously or in response to painful stimuli.

Death is defined as cardiac asystole or arrest, whether occurring spontaneously or upon removal of mechanical support.

Electrocerebral silence may be defined as an EEG record with no biological activity over 2μV between scalp or referential electrode pairs 10 or more centimeters apart with interelectrode resistances between 100 and 10,000 ohms (with needle electrodes, 100 and 100,000 ohms) for a period of 30 minutes.

Respirator brain is that state of the brain, present, usually after 24 hours of artificial respiration, characteristically described as soft in spite of fixation, congested, dusky in color, edematous (especially the cerebellum that may be moulded about the brainstem), and microscopically showing acidophilic, swollen neurons with pyknotic nuclei, dilatation of cerebral vessels with edematous endothelium and perivascular hemorrhages, and little or no inflammatory reaction.

Survival implies that the body is able to take care of its needs without mechanical support. This may be at vegetative or normal levels of life.

In testing the sets of criteria of cerebral death, their accuracy (the predictability of clinical and EEG lack of biological activity), scope (how many cases of cerebral death without clinical or electroencephalographic evidence of biological activity are not included), and practicability (the feasibility of the criteria in a clinical setting) will be assessed.

Analysis of the study data indicated that: provided all appropriate diagnostic and therapeutic procedures have been performed, cerebral unresponsivity, apnea, absent cephalic reflexes, with dilated pupils and electrocerebral silence (ECS) accurately predict death and eventual cardiac arrest in all cases (2). However, since the critical decision required was not the prediction of death nor a statement of the probability of survival, great care had to be taken to dissociate the diagnosis of brain death from the prognosis for eventual outcome.

In order to distinguish those about to die from patients whose brains were already dead, an independent confirmatory test was considered highly desirable by the clinical investigators. An assessment of cerebral circulation was deemed the most suitable parameter to be exploited because of two major problems encountered in the course of the prospective study (3).

The first major issue involved the proof of accuracy of the clinical diagnosis. Although the constellation of gross and microscopic features termed "respirator brain" is considered presumptive evidence of death at some time prior to termination of artificial resuscitation by many neuropathologists (4), certain biological and logistical factors limit the usefulness of traditional clinicopathological correlation as applied to brain death.

Morphological pathology varied considerably in the cases autopsied from this study (5). The concurrence between postmortem changes of "respirator brain" and electrocortical silence in the last electroencephalogram was imperfect. Only 54 percent of patients who died with

ECS showed morphological changes consistent with the "respirator brain." Nine respirator brain specimens, on the other hand, were obtained from patients whose final cardiac arrest occurred when the most recent EEG showed biological activity.

Neither did the duration of respirator dependency correlate precisely with the incidence of the respirator brain (5). Four patients showed respirator brains after less than 12 hours of mechanical ventilation. These discrepencies may be due to the uncontrolled logistical variables in latency between ictus and accession to the study and to the unknown mechanisms and time course through which biological death proceeds to morphological change in tissue. Therefore, the pathological findings could not reliably prove the accuracy of the clinical diagnosis of brain death using generally available techniques of gross description and light microscopy.

The second and more significant problem identified in the prospective study was the detection and interpretation of the influence of drugs known to depress nervous system function. Low levels of central nervous system (CNS) depressants were detected in blood samples drawn during the initial workup of patients in whom the history of ingestion was unclear, raising the total number in whom drugs were known to be involved to 61, whereas only 36 persons entered the study with an initial clinical diagnosis of intoxication. Furthermore, during a comprehensive analysis of blood samples from this same series of patients done at an independent investigative laboratory, 87 patients were shown to harbor measurable amounts of central nervous system depressants in their sera. Table 2 summarizes the qualitative and quantitative findings in 313 blood samples sent to a central laboratory at NINCDS for screening. These findings indicate that in 26 patients one of the other primary diagnoses listed in table 1 was complicated by drugs taken before or given after their cerebral catastrophe. Even in known cases, there was poor correlation between quantitative blood levels and depth or duration of coma, probably because of uncontrolled variation in sampling time after ingestion and differences in plasma clearance times among the various depressant drugs. Therefore, it became necessary for the investigators to actively pursue the history of drug ingestion and, even if only minute amounts of intoxicants were found in the blood, to instigate appropriate therapy.

Despite such unresolved conceptual and operational problems, a number of sets of criteria have been proposed in the scientific literature for the pronouncement of brain death, each with certain merits and each based upon a different biomedical principle. Of these, the Harvard Criteria are the best known (6), but the Minnesota Criteria (7), the formula derived from a recent Japanese Study (8), and criteria recommended for use in Scandinavia (9) and other European countries are alternative prototypes.

These formulas were usually developed by consensus and were based on retrospective experience and literature reviews. Few have ever been tested in large prospective series of patients for scope, defined herewith as the frequency with which comatose, apneic patients meet such criteria; for accuracy, the reliability with which the criteria permit a diagnosis of death using clinical or morphological standards; and for practicability in modern general hospital settings.

Adequate scope becomes an important feature for criteria to be used in the prompt identification of fresh cadaver organs for transplantation. Nonetheless, accuracy must be absolute despite the desirability for broad scope and facile application.

This present review tests the previously reported alternative sets of criteria for scope, accuracy, and practicability using the comprehensive data bank prospectively acquired in the course of the NINCDS Collaborative Study of Brain Death (3).

HARVARD CRITERIA

In its report (6), the Harvard Committee on Irreversible Coma set forth the characteristic clinical and encephalographic features of the nonfunctioning brain. The committee required that hypothermia and drug intoxication be ruled out before the suggested criteria be applied. While hypothermia posed no particular problem in the NINCDS Study, the unreliability of the history of ingestion and quantitative drug levels in sera have already been mentioned. The basic features of the Harvard Criteria are shown in table 3.

In order to distinguish between cerebral death and irreversible coma, the Committee required that the physical signs and the EEG silence persist for 24 hours. Death was therefore equated with the permanently nonfunctioning brain and could be safely pronounced when the 24-hour requirement, indicative of permanence, was met.

If these criteria are applied to the prospective series of 503 cases, the 61 cases of diagnosed drug involvement must be eliminated. Of the remaining 442, 32 had an absence of cephalic and spinal reflexes for 24 hours, but only 19 or 4 percent of the entire series had electrocerebral silence over the same interval. Yet, 96 percent of the prerequisite group died, two-thirds showing electrocerebral silence.

Obviously, these criteria, although 100 percent accurate and practical, have a narrow scope.

Clinicopathological Correlation: Of the 19 patients meeting the Harvard Criteria for 24 hours, 14 were autopsied. In 8 of the 14 autopsied, respirator brain was diagnosed.

MINNESOTA CRITERIA

A number of authors have suggested that the criteria of cerebral death should only be applied to those cases in which the nature and extent of the brain damage is known to be irreparable and that, in such cases, the physical findings and clinical judgment of the physical are adequate for pronouncement of death.

In the prospective study data, the diagnostic categories of cerebral trauma, cerebrovascular disease, CNS infection, and cerebral neoplasm met the basic prerequisite for the Minnesota Criteria (7), shown in table 4. There were a total of 273 such cases.

The first three criteria were met on one occasion by 180 cases in this series; of these, 17 had biological activity in the EEG at the time they met the criteria. Although 141 patients met all three criteria for a period of 12 hours, 11 of these did not have ECS at either the initial or 12-hour examination.

On the basis of these criteria, 8 percent of the cases would have had resuscitative efforts stopped while the EEG still had evidence of cerebral electrical activity. Nonetheless, the criteria if met predicted eventual death in all patients in this series.

Clinicopathological Correlation: "Respirator brain" was diagnosed in 51 percent of autopsied cases meeting these criteria. One would conclude that the accuracy of the criteria based upon EEG evidence of a nonfunctioning brain is 92 percent and the scope is 67 percent.

JAPANESE STUDY CRITERIA

The criteria used for brain death in Japan assume that a gross primary lesion has been diagnosed and invoke as the signal of death the principle of cardiovascular collapse sustained for 6 hours (8). (See table 5.)

If one applies these criteria to the collaborative study series of 503 cases (2), in the categories of cerebral trauma, cerebral vascular disease, infections of the brain and brain tumors, there were 273 cases. Only 11 cases (4 percent of the entire population) met all the Japanese Study Criteria including hypotension for 6 hours. If the requirement of a fall of 40 mm of mercury in blood pressure were omitted, the scope is expanded to only 36 patients having a persistent 6-hour hypotension below 80 mm Hg.

Clinicopathological Correlation: Of the 164 patients meeting the Japanese Study Criteria excluding hypotension, autopsies were made on 84 cases and 52 of these (62 percent) had respirator brains.

Although the scope of the Japanese Criteria is extremely limited, no patient meeting the criteria survived or had evidence of cerebral viability by EEG standards at the time cerebral death was declared; hence, the accuracy of 100 percent.

SCANDINAVIAN CRITERIA

In Europe, another definition of cerebral death had been introduced, namely, that of total ischemic infarction of the brain (9, 10).

The criteria shown in table 6 are based on this premise. They introduce the concept of circulatory failure limited to the brain as the discriminative principle separating cerebral death from the dying process. These criteria are attractive because a) they require a minimal time lapse between serious consideration of the diagnosis of brain death and definitive diagnosis of total cerebral infarction, and b) taken collectively, they are independent of etiology, including toxic agents.

Unfortunately, these criteria could not be adequately tested against the prospective series because, although a majority of cases in the study had primary intracerebral pathology which might have warranted diagnostic contrast studies, only 17 angiograms were performed (1, 3). Although some European investigators have asserted that failure of cerebral perfusion is common to all cases of cerebral death, there are a few exceptions to their rule (11).

CRITERIA PROPOSED BY THE NINCDS COLLABORATIVE STUDY

The criteria formulated in table 7 were recommended for further testing by the participating investigators in the Collaborative Study. They constitute a pragmatic adaptation of previously reported scientific principles and encompass the concepts of both electrocortical silence and the absence of cerebral perfusion, determined independently. The risk of error introduced by drug intoxication is minimal for although barbiturate drugs are known to both suppress the electrical output of the brain and reduce cerebral blood flow, it seems unlikely that cerebral perfusion would be compromised in the absence of massive intracranial hypertension.

Because angiography was considered an invasive and stressful technique and rarely used in the evaluation of brain death suspects in this country, a number of other indirect methods of assessing cerebral perfusion were suggested for trial.

1. Bolus Transit Curves.--Braunstein et al. (12) used portable detector equipment to evaluate the Oldendorf technique--the strip record of the passage of an intravenous bolus of ^{99m}Tc pertechnetate through the head--as an indicator of cerebral circulation in 68 cases. Using the femoral artery circulation as a control they found that with an intact cerebral circulation, a pronounced curve was seen in both cephalic and femoral records; with an absence of cerebral circulation, the cephalic record was flat and the femoral had a passage curve. When the results were definite for absence of intracranial circulation (in three-fourths of the cases), there was 87 percent correlation with electrocerebral silence.

2. Echoencephalography.--Pulsation of the midline echo is believed to result from the internal carotid pulsations within the intracranial cavity. Accordingly, it has been suggested that there may be a direct correlation between absence of the pulsation of the midline echo and the absence of cerebral circulation (13). In the prospective Collaborative Study series, the technique was used in only 17 cases; when pulsations were absent, biological EEG activity was absent (14).

3. Ophthalmoscopic Findings in Cerebral Death.--The presence of blood flow in the retinal arteries has been suggested as an index of flow in the intracranial portions of the internal carotid arteries (15, 16, 17). With an absent or depressed circulation, clumped erythrocytes in the retinal vessels give the appearance of strings of sausages, stationary or moving slowly in the vessels (sludging). Although sludging was present in only 20 percent of the patients suspected to have cerebral death, its occurrence was associated with ECS in 75 percent of cases and invariably with a fatal outcome.

Although none of the indirect methods for assessment of cerebral circulation have been validated by standard methods of determining cerebral blood flow, preliminary data analyses and literature reviews indicate that an absent cerebral radionuclide bolus effect, a nonpulsating midline echo (14), or retinal sludging (16, 17), indicate the absence of cerebral perfusion with an accuracy of at least 80 percent. Obviously, additional studies of these techniques are needed to validate their relationship to cerebral blood flow and electrocerebral silence.

DISCUSSION

The term "cerebral death" was introduced on Parisian wards to describe patients in deep coma who required artificial respiration to sustain even vegetative existence. It was natural to assume that such patients had a dead brain. Semiological difficulties arose when attempts were made to define the boundaries of coma and when autopsy studies of the brains of these patients showed not a uniform panencephalopathy but varying degrees of pathological change. It was then apparent that "cerebral death," like some other terms, had grown out of a concept that never had acquired a precise clinical or pathological basis. As a result, arbitrary standards that were considered essential for the diagnosis of cerebral death were set up by organizations, committees, and even individuals. Although their inadequacies became obvious when patients meeting these criteria survived, there was no simple way to determine when the criteria were overly restrictive.

Any validation of the criteria of cerebral death is hampered by the absence of a precise, objectively defined concept of the condition and by the lack of a pathological substrate. Theoretically, the absence of all clinical manifestations of cerebral function should be apparent from a neurological examination, although there might be some question as to the distinction between cerebral and spinal activity. If, in addition, there is no evidence of biological activity in the EEG, one might assume a total inactivity of the brain. But that the state is permanent and represents a dead brain cannot be so easily established since a number of conditions will temporarily depress, or even abolish, nervous activity. Unfortunately, the brain's precise tolerance to variable degrees and durations of intoxication, anoxia and acidosis are not determined for the normal adult and even less is known regarding the susceptibility of children and older people. Accordingly, even if the presence of a drug or drugs in the blood can be established, without knowledge of precise, time integrated, dose-response curves for each agent, the actual blood level may be of relatively little value in the assessment of the total problem.

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The absence of a uniform pathological substrate is also a deterrent to the definition and diagnosis of a dead brain. The respirator brain only in its late stages may be considered a recognizable neuropathological state common to many but not all dead brains. There are obviously gradations between the normal and the respirator brain dependent upon factors mainly unknown. For these reasons an independent test of brain viability seems desirable.

Since the pathophysiology of many cases of brain death seem to relate to cerebral infarction or anoxic encephalopathy, a measure of cerebral blood flow or oxygen consumption would seem the logical basis for the diagnosis of a dead brain. Unfortunately, quantitative, direct measurements of cerebral blood flow are time consuming, cumbersome, and fraught with error except in the most experienced hands. Moreover, quantitative data recorded in sophisticated laboratories still permit doubt over the brain's capacity for energy metabolism at reduced cerebral perfusion pressures and hypoxemia (18) and during dissociations among intracranial pressure, cerebral blood flow, rate of oxygen consumption, and autoregulation (19). In certain cases of prolonged coma, Heiss has reported specific reduction in flow to the cerebral hemispheres caused by lesions in the brainstem (20). Conversely, "luxury perfusion" has been described in conjunction with electrocerebral silence and the clinical signs of brain death (11). One might conclude, therefore, that quantitative direct measurements of cerebral blood flow and metabolism, at the present state of the art, have limited application to the practical clinical question of brain death (21). As in many other practical applications of scientific principles, one or more of the indirect qualitative methods, listed in table 8, may prove of greater diagnostic value at the bedside. A combination of clinical tests, EEG and indirect assessments of cerebral circulation, allows a diagnosis of a dead brain to be made virtually within the time needed to carry out these tests--perhaps an hour or two--with practically no chance of error.

Although angiography is a reliable and readily available technique for assessment of intracranial circulation, the procedure is invasive and introduces additional risk in the management of moribund patients. To minimize risk and the inconvenience imposed by the need to transport critical patients to the radiology suite, a number of alternatives for assessing cerebral perfusion have been suggested. These include: 1) bolus transit curves, 2) echoencephalography, and 3) ophthalmoscopic findings in retinal circulation.

A critical analysis of several published sets of criteria for brain death is summarized in table 9. This retrospective test of these criteria on comprehensive prospectively acquired data indicates the need for a multifactorial basis for the diagnosis of cerebral death. It seems that any criterion applied at a point in time and based upon a single scientific principle--be it clinical history and findings, electrographic examinations, or even cerebral blood flow determinations--will fall short of absolute accuracy. Repetitive findings using a single test system over time provide greater confidence for the diagnosis of brain death. But the currently required latencies, logistical incumbencies and risks inherent in application of previously reported formulas severely limit their utility. Assessment of the multifactorial determinants of clinical, electrophysiological, and cerebral circulatory findings offers the most rational and practical opportunity to reduce the latency yet insure the accuracy of the diagnosis of brain death.

Table 1

PRIMARY DIAGNOSIS--NUMBER OF CASES

Diagnosis	Total Number of Cases
Cardiac Disease	105
Cerebral Trauma	94
Cerebral Thrombosis	25
Cerebral SAH	34
Cerebral Embolism	8
Cerebral Haem	74
Cerebral (other)	9
CNS Infect	17
Exog. Intox.	36
Metab. Disorder	36
Neoplasm	12
Other	53
Total	503

Table 2

ANALYSIS FOR CNS DEPRESSANT DRUGS IN 313 BRAIN DEATH SUSPECTS

		Concentration (ug/ml)					
Drugs	**Total**	**<10**	**10-29.9**	**30-59.9**	**60-99.9**	**100-199.9**	**>200**
Phenobarbital	54	36	11	5	1	1	--
Secobarbital	4	1	3	—	—	—	—
Amobarbital	2	2	—	—	—	—	—
Pentobarbital	6	3	2	1	—	—	—
Glutethimide	1	—	1	—	—	—	—
Meprobamate	4	—	2	—	1	—	1
Ethchlorvynol	2	—	—	1	1	—	—
Alcohol (mg/%)	14	—	6	4	—	2	2
Total cases with drugs	87	42	25	11	3	3	3
Total cases without drugs	(226)						

Note: 3 samples contained combinations of two barbiturates
1 sample contained 8 ug/ml methaqualone

Table 3

HARVARD CRITERIA

Prerequisites:	Absence of -- hypothermia drug intoxication
Criteria :	Unresponsive coma Apnea Absence of reflexes
Confirmation :	Isoelectric electroencephalogram
Duration :	24 hours

Table 4

MINNESOTA CRITERIA

Prerequisite:	Irreparable brain damage
Criteria :	No spontaneous movement Apnea Absent brainstem reflexes
Duration :	12 hours

Table 5

JAPANESE STUDY CRITERIA

Prerequisite:	Gross primary brain lesion
Criteria :	Deep coma Apnea Bilateral dilated pupils Absent pupillary and corneal reflexes Isoelectric electroencephalogram 40 mm Hg fall in blood pressure with persistent hypotension
Duration :	6 hours

Table 6

SCANDINAVIAN CRITERIA

Prerequisites	:	None
Criteria	:	Unresponsive coma Apnea Absence of all cerebral functions, including all brainstem reflexes Isoelectric electroencephalogram Nonfilling of cerebral vessels on 2 injections 25 minutes apart
Duration	:	25 minutes

Table 7

COLLABORATIVE STUDY CRITERIA

Prerequisites:	Diagnostic and therapeutic procedures completed
Criteria :	Unresponsive coma Apnea Absent cephalic reflexes Dilated pupils Isoelectric electroencephalogram
Confirmation:	Absence of cerebral circulation
Duration :	30 minutes, provided confirmatory test is performed 6 hours after cerebral insult

Table 8

INDIRECT METHODS

FOR

ASSESSMENT OF CEREBRAL CIRCULATION

Angiography - 4 vessel

Bolus curves

Echoencephalography

(midline pulsation)

Retinoscopy (sludging)

Table 9

CRITERIA FOR DIAGNOSIS OF BRAIN DEATH—A COMPARATIVE ANALYSIS

	Harvard	Minnesota	Japanese Study	Scandinavian	NINDS Collaborative Study
PREREQUISITES FOR ACCESSION					
Absence of hypothermia	+			*None*	*Diagnostic and therapeutic procedures completed*
Absence of drugs	+				
Irreparable brain damage		+			
Gross primary brain lesion			+		
CRITERIA					
Deep unresponsive coma	+		+	+	+
Apnea	+	+	+	+	+
Absence of spinal and cephalic reflex activity	+				
Absence of brainstem (only) reflex activity		+	+	+	+
Hypotension			+		
Electrocerebral silence	+		+	+	+
No spontaneous movement		+			
Dilated pupils			+		+
Nonfilling of cerebral vessels in 2 injections 25 minutes apart				+	
DURATION	24 hrs	12 hrs	6 hrs	25 mins	30 min period 6 hrs post ictus
SCOPE	4%	67%	4%	6%	Insufficient Data
ACCURACY	100%	92%	100%	Insufficient Data	Insufficient Data
PRACTICABILITY	Good	Good	Fair	Poor	Good

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